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THE COVER

The imaginative blood smear which is shown on this month's cover contains small photographs as white blood cells. These represent a few of the clinical aspects of 'blood'. Although complex electronic machines are available for such procedures as hemoglobin determinations or RBC counts, they are not included in the composite picture. Machines exemplify the expensive, mechanical laboratory approach to a study which must remain in most cases a personal skill of the physician and be quickly available to him in the critical period of examination prior to diagnosis.

D.P.A.

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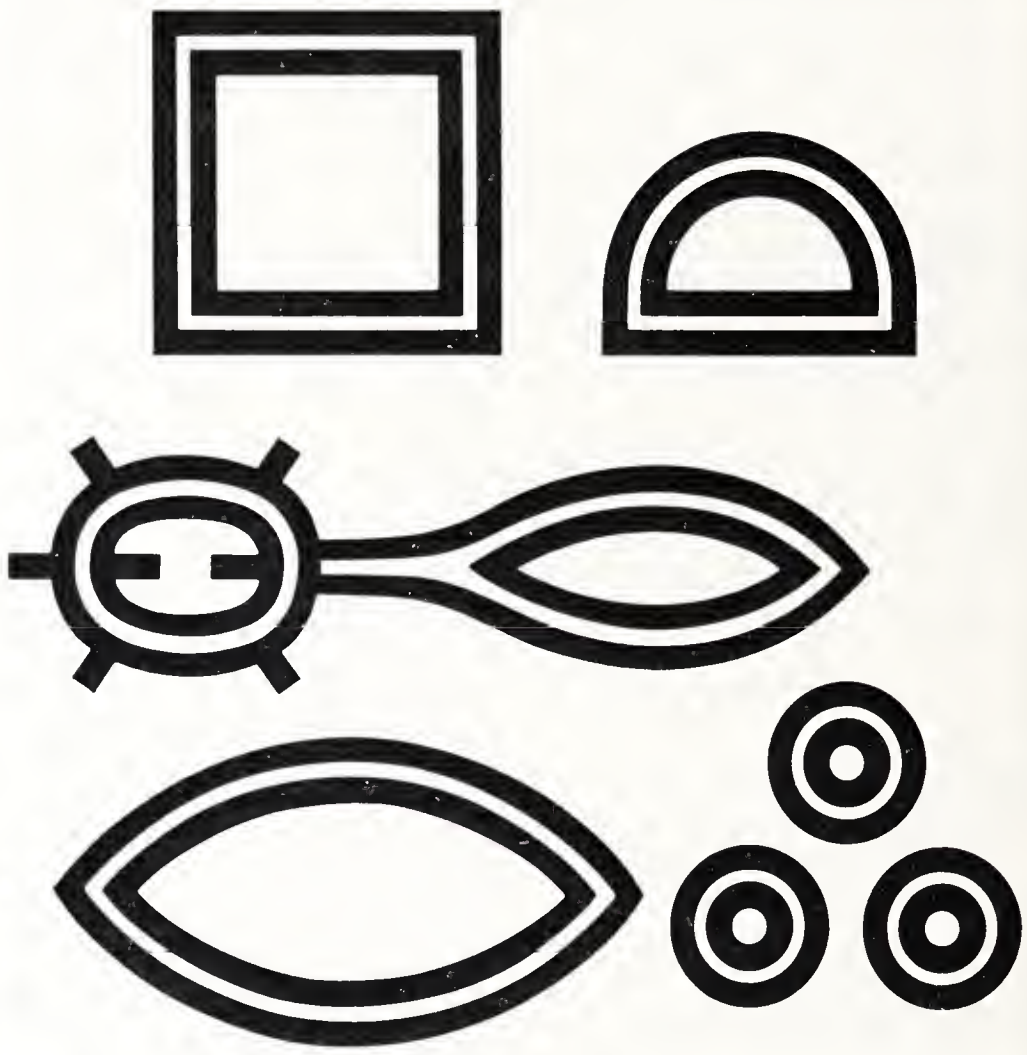

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Illustrations are included by arrangement with the Editor. Drawings should be on white paper in black ink.

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Editorials

BLOOD — A MYSTERIOUS MIRROR

Throughout the history of mankind, through ages poorly understood by many of us today, there has been a liquid mystery encased within the channels we call blood vessels. To the mystery of its true purpose has been superimposed the element of fear and respect present even today in the eyes of many, when through combat or chance, trauma or trivia, it oozes from its tubular prison and is shed. Is it any small wonder that history reveals a significant place of honour attributed to this "red river of life" in cultures both primitive and civilized. With mixed feelings of dread and awe the symbol of blood enters into many occult practises, superstitious ideas, and religious rites.

Today, in the general field of medicine there is a similar attitude of respect for blood, but for reasons different. The man with a scientific eye recognizes the importance of blood as a useful tool in his diagnostic armamentarium as it reflects not only the functioning of various aspects of the hemopoietic system, but as well, most of the body organ systems and their relative state of function or malfunction. By means of a multitude of tests in hospital laboratories across the country samples of blood — undoubtedly exceeding in number any other sample of human tissue — are examined as an aid in assessing the patient's medical state.

The importance of an adequate understanding of the hemopoietic system, the various diseases affecting it directly, and its function as a mirror of body chemistry need not be stressed further. It is to this end that the articles in this issue have been compiled, but to assume that coverage of the individual aspects of hematology, or of the field as a whole has been exhaustive, would be presumptuous.

J.R.T.

NEWS ITEM:

Meeting the challenge of a growing need for more doctors, the University of Toronto expands the first medical year to 180 students.

WHERE IS THE NEXT PLATEAU?

It is generally accepted that the framework of medical education is constructed in the form of a series of ascending steps. It is probably more correct to view the whole of medical education, including medical school, as a giant ramp of increasing knowledge and skill. For all except one group in medical school, the steps are clearly defined: one must simply move up from one plateau to the next, year after year.

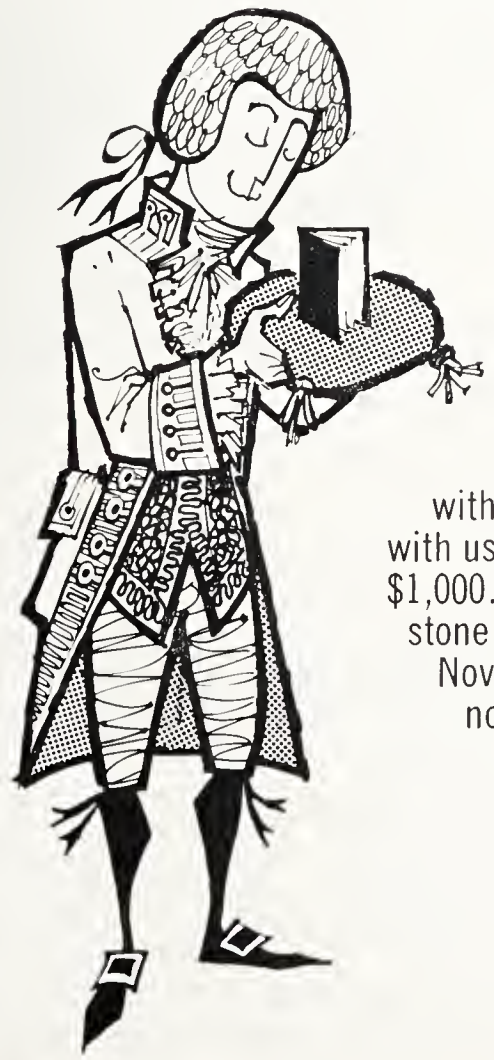
Problems arise for the final year medical student. He may find himself moving towards the edge of what appears to be the last plateau and beyond that there seems to be either an insurmountable wall or a black sea of unknown experience.

After careful analysis of the answers of 'those who have gone before', he learns that there *is* a next plateau. He may also catch a glimpse of the sort of things that may be in store for him in an internship — enough at least to realize that there is not just one next plateau, but a multitude. These plateaus are of various heights and strengths, and involve a whole spectrum of training.

The lower plateaus are the controlled programs where teaching plays a large part. Supervision is never too far away and the interne sometimes has more time for reading and consolidation of his knowledge. Internes in this type of plan may complain about too much 'scutwork'. The higher plateaus usually entail a greater amount of responsibility and *doing* rather than *viewing*. Although teaching may be restricted with this type of internship, this writer feels that responsibility is a stimulus to learning and that he would benefit by the added experience.

Whatever the choice, it is well to remember that these variously sized plateaus vary in strength or stability. This feature is much more difficult to judge and may not be apparent until the young doctor is engaged in the next phase of his training. In the final analysis, it is this metaphorical strength which is important. All must aim for a 'strong' internship as a basis for future training, but each must decide for himself.

J.D.G.



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Anemias of Infancy and Childhood

John Lackner 6T3

After considering the general features of anemia, the author classifies the anemias which occur in the young and discusses the more common of these.

Anemia may be defined as a condition in which the concentration of hemoglobin is reduced, with or without a concomitant reduction in the number of red blood cells. The resultant defect in physiology is a decrease in the oxygen carrying capacity of the blood and a reduction in the oxygen available to the tissues for metabolism.

GENERAL CONSIDERATIONS

Anemia in childhood is unique. As in an adult, anemia arises when one or more of the following conditions exists: (1) Increased blood destruction, (2) Increased blood loss, (3) decreased blood production. The uniqueness arises from the fact that a child grows very rapidly. His hemopoietic system, along with the majority of his other body systems, is straining at maximum capacity, to keep pace with general development. Until he is seven years old, a child has little or no yellow bone marrow which he can mobilize for hemopoietic duty in a crisis. Thus, an insult to his hemopoietic integrity can not be dealt with as efficiently as it can be in an adult.

To evaluate the blood picture in any given child, intelligent interpretation requires a knowledge of the normal values in the various age groups. The expected values are shown in figure 1.

Accurated diagnosis is most important. After recognizing the presence of an anemia, the physician must use his intellect and a few simple laboratory procedsures to specifically locate the anemia in an etiologic classification, before instituting active treatment.

A thorough *history* is essential. Interrogation should include the following: onset of pallor, birth weight, diet, appetite, irritability or easy fatiguability, blood loss, jaundice, infections, exposure to chemicals (including drugs) and radiation. In doing the *physical examination* the physician should look for pallor (conjunctiva and nail beds), splenonegaly, lymphadenopathy, signs of a hyperdynamic circulation, (cardiomegaly, hemodynamic murmurs, arterial bruits and a wide pulse pressure), and evidence of bleeding disorders (petichiae, purpuric spots and ecchymoses). Many anemias have specific clinical signs and these will be discussed later.

Laboratory tests are an invaluable adjunct to the study of anemia. The essentia! procedures include determination of the hemoglobin cencentration, red blood cell count, hematocrit, and reticulocyte count. Visual examination of the blood smear is imperative. It shows the effect that the etiologic factors have on the morphology of the red blood cells. One may classify the anemias according to the size of the red cells; normocytic, microcytic, and macrocytic, and to the hemoglobin concentration in individual cells, normochromic. (Hyperchromic anemias do not exist.) However, there is almost always a degree of anisocytosis and poikilocytosis associated with anemia. Thus, one often needs substantiation of the visual impression gained from the smear. Mathematical verification is possible by manipulation of the red cell count, hemoglobin concentration and hemotocrit, as follows:

(1) Mean Corpuscular Volume (MCV)
(units are cubic microns)

$$MCV = \frac{\text{Hematocrit (\%)} \times 10}{\text{R.B.C. in millions/cu. m.m.}}$$

Normal range = 80-94 cubic microns
— macrocytes have a MCV greater than 94
— microcytes have a MCV less than 80.

(2) Mean Corpuscular Hemoglobin (MCH)
(units are micro micrograms)

$$MCH = \frac{\text{Hemoglobin (Gm/100 ml.)} \times 10}{\text{R.B.C. in millions/cu. m.m.}}$$

Normal range = 27-32 micro micrograms
Hyperchromic cells have a MCH greater than 32.
Hypochromic cells have a MCH less than 27.

(3) Mean Corpuscular Hemoglobin Concentration
(express as a percentage)

$$MCHC = \frac{\text{Hemoglobin (Gm/100 ml.)} \times 100}{\text{Hematocrit (\%)}}$$

Normal range (normochromic) = 32%-38%
Cells are hypochromic if MCHC is less than 32%
Cells are hyperchromic if MCHC is greater than 38%

It is often desirable to gain information about the activity of the bone marrow, both in making a diagnosis and in following the course of treatment of an

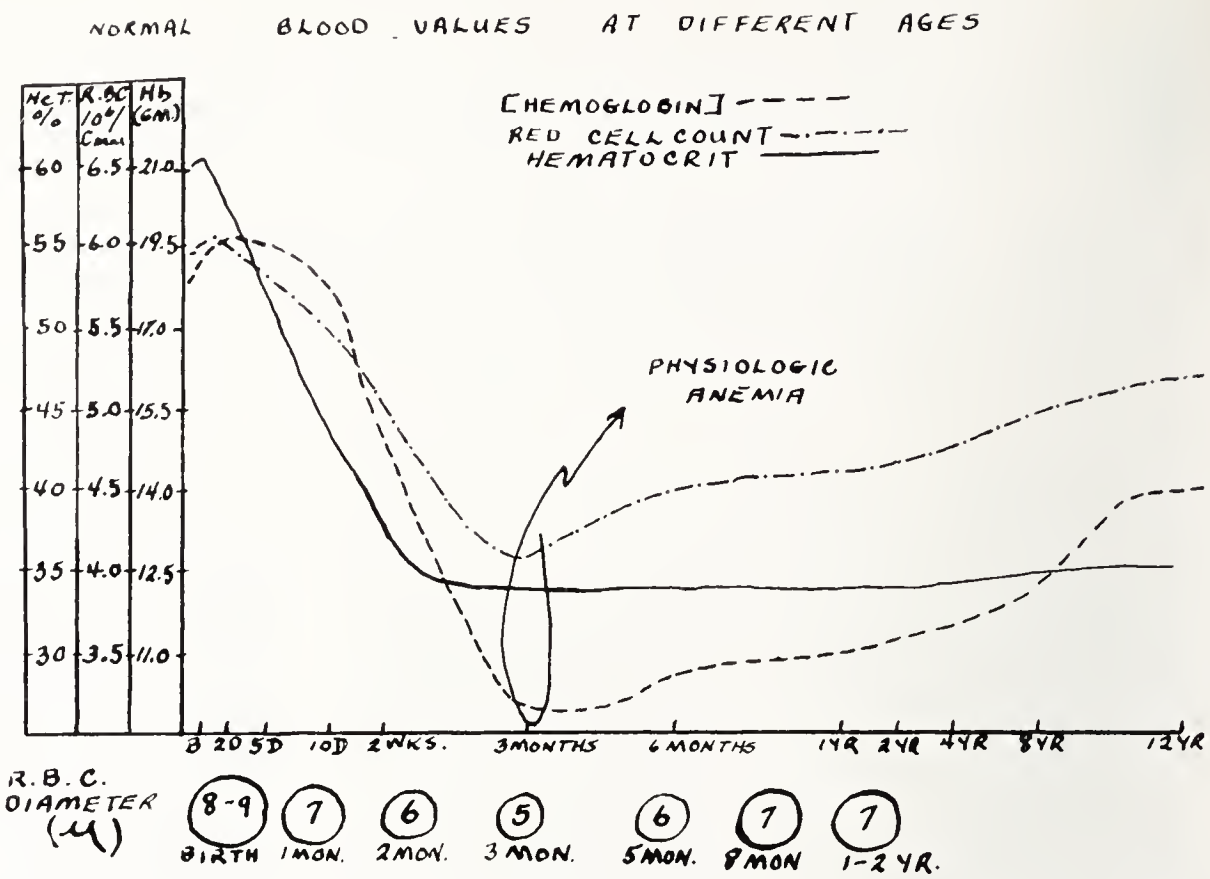

NORMAL BLOOD VALUES AT DIFFERENT AGES
HCT. % R.B.C. 10⁶/Cmm Hb (GM)
[HEMOGLOBIN] - - - -
RED CELL COUNT -·-·-·-
HEMATOCRIT ——
60 6.5 21.0
55 6.0 19.5
50 5.5 17.0
45 5.0 15.5
40 4.5 14.0
35 4.0 12.5
30 3.5 11.0
PHYSIOLOGIC ANEMIA
B 20 5D 10D 2WKS. 3MONTHS 6MONTHS 1YR 2YR 4YR 8YR 12YR
R.B.C. DIAMETER (μ)
8-9 7 6 5 6 7 7
BIRTH 1MON. 2MON. 3MON. 5MON. 8MON 1-2 YR.

Fig. 1. Values for hemoglobin, hematocrit, red cell count and diameter from birth to 12 years

Taken in part from Nelson, Textbook of Pediatrics, Seventh Edition, 1959, W. B. Saunders Co., Page 931.

anemia. This can be accomplished in two ways; indirectly, via a *reticulocyte count,* and directly, by bone *marrow aspiration.*

An anemia due to increased blood loss or destruction will be associated with an elevated reticulocyte count, whereas, if the anemia is secondary to decreased erythropoiesis, the reticulocyte count will be depressed. In surveying a bone marrow smear, one must observe the cell types of the platelet and red and white cell lines. Most often, but not universally, an affliction of one cell type is accompanied by some alteration in the other cellular series.

In difficult cases, the physician may also have to employ the following tests to make a diagnosis:

1. Stool benzidine test
2. Coomb's test
3. Red eell fragility test
4. Hemoglobin electrophoresis
5. Serum bilirubin and BUN
6. Stool urobilin
7. Serum iron and iron binding capaeity
8. Bone marrow iron

CLASSIFICATION

To illustrate the potential frequency of anemia in this age group, a fairly comprehensive classification based on etiology follows:

1. Blood Loss (causes an iron defieiency anemia)
   - A Aeute hemorrhage (initially normochromie, normocytic but beeomes hypochromic microcytic) plaecntal hemorrhage, placental vascular abnormalities, blood loss from the umbilical cord, circumcision, hemorrhage into large organs, fraetures, trauma, hemophilia. thromboeytopenie purpura, rupture of esophageal varices.
   - B Chronic hemorrhage (hypochromic microcytic) gastrointestinal ulcerations, polyps, esophageal varices, coagulation disorders, epistaxis, hookworm disease, genitourinary bleeding.
2. Execssive Blood Destruction (variable morphologieal changes.)
   - A Intracorpuscular or Intrinsie Defects (usually hereditary)
     - (1) Hereditary spherocytosis
     - (2) Congenital non speroeytic hemolytie anemias
     - (3) Thalassemia (Cooley's anemia)
     - (4) Sickle Cell Anemia
     - (5) Hereditary hemoglobinopathies (C, D, E, G, H, I, and others)
     - (6) Hemolytic anemia due to enzyme deficieney apparent after administration of drugs and other agents; primaquine, naphthaline, fava bean
     - (7) Paraxysmal noeturnal hemoglobinuria (not hereditary)
   - B. Extraeorpuscular Defeets (usually aequired)
     - (1) Duc to antibodies (a) Autoimmune Antibodies (b) Isoagglutinins (erythroblastosis, mismatched transfusion).
     - (2) Symptomatie hemolytic anemias with Hodgkin's disease, lymphosarcoma, renal disease, lupus erythematosis etc.
     - (3) Paroxysmal cold hemoglobinuria
     - (4) Acute aequired hemolytic anemia (Lederer's anemia)
     - (5) Mareh hemoglobinuria
     - (6) Miscellaneous causes: Infection with parasitization, (malaria, Oroya Fever) Chemical and physieal agents, Vegetable substanecs, Drug sensitivity, Severe burns

3. Decreased or Impaired Production
   A. Hypoplastic — (usually normochromic normocytic)
      1. Idiopathic (a) Physiologic anemia of infancy (b) Pure red cell aregenerative anemia
      2. Acquired (a) Due to infections, drugs, chemicals, toxins, autoimmune and allergic states. (b) Aplastic crisis in course of hemolytic syndromes (hereditary spheroeytosis, sickle cell anemia). (c) Suppressive effect of multiple transfusions.
   B. Aplastic Anemia (usually normochromic normocytic)
      1. Idiopathic: Congenital aplastic anemia with other congential abnormalities (Fanconi type), without associated abnormalitics.
      2. Acquired: (a) Anemia due to antimicrobial and other chemotherapeutic agents (chlormycetin) (b) Due to industrial and household chemicals (c) Due to irradiation (d) Miscellaneous: infections, endocrine, factors, chronic azotemia, hypothyroidism, bone marrow invasion, or replacement (myelophthisic anemias of leukemia, Hodgkins, Gaucher's, osteoporosis, etc.)
   C. Deficiency of Substances required for red cell and hemoglobin production due to
      (1) Inadequate stores at birth-prematurity
      (2) Inadequate diet
      (3) Inadequate intestinal absorption: sprue, idiopathic steatorrhea, celiac disease, congential strictures, gastrointestinal resections, chronic diarrhea.
      1. Iron (hypochromic microcytic anemia)
      2. Vit. B_{12}, folic acid, ascorbic acid (macrocytic anemia with megaloblastic bone marrow)

COMMON ANEMIAS OF THE YOUNG

Physiologic Anemia of the Newborn

Beginning a few days after birth, the hemoglobin and red cell levels drop, reaching a minimum at 2 to 3 months in the full term infant. (see figure 1). A normochromic, normocytic anemia develops. The iron liberated by red cell destruction is stored for later use in rebuilding hemoglobin. With the changeover from the placenta to the lung as a source of oxygen, there is no need for the elevated hemoglobin values found at birth to maintain a normal post-natal oxyhemoglobin content of the blood, so that erythrogenesis and hemoglobin production are retarded until such a time as the hemoglobin level drops to approximately 11 gm. %[2]. Any decrease below this point induces increased hematopoietic activity. With the resumption of active erythropoiesis, reticulocytes appear and the circulating mass expands. The amount of hemoglobin synthesized will be limited by the iron which has accumlated in the stores during the post-natal drop in hemoglobin. Increasing body weight and blood volume obscures the improvement in the hemoglobin concentration during the recovery period. The supply of iron becomes strained with rapid growth, and unless adequate dietary iron is supplied, at about 6 months of age, an iron deficiency anemia develops.

Iron Deficiency Anemia

This is the most common nutritional deficiency in children and usually occurs between the ages of 6 and 24 months. The most common cause is a birthweight of less than 3 kg.[3] Clinically, infection may highlight a latent anemia. The usual signs of anemia are present. Dramatic sheet-like pallor may develop, and in older children, atrophic glossitis, dysphagia and koilonychia occur infrequently.[1]

Laboratory Data. This is a hypochromic, microcytic anemia. The hemoglobin concentration is reduced to 3 to 9 gm. %, and the red cell count ranges from 3 to 5 million. The hematocrit is reduced. The MCH is less than 27 micrograms and the MCHC is less than 30%. The blood smear shows microcytes, poikilocytosis, anisocytosis and target cells. Reticulocytes are normal or reduced and red cell fragility is normal or decreased slightly. The bone marrow exhibits erythroid hyperplasia and an almost complete absence of stainable iron or hemosiderin, indicating diminished iron stores. The serum iron is reduced, varying from 10 to 60 micrograms per 100 ml. (normal, 120 micrograms). The latent serum iron-binding capacity is increased to greater than 450 micrograms (normal 250 micrograms per 100 ml.) The "brush cut" sign may be seen on radiologic examination of the skull in patients with chronic iron deficiency anemia, especially in premature infants and twins.[4]

Treatment. Thorough treatment of etiologic factors such as faulty diet, blood loss, etc. is essential, in addition to supplemental iron therapy which must be sufficient to correct the anemia, and replenish iron stores.

Dose and Administration of Iron. Ferrous iron salts for *oral administration* are the usual regime. Ferrous sulphate is the least expensive and is available as an elixir for infants and as 3 grain tablets for older children. Approximately 10 grains is the daily dosage. Full therapeutic doses should be given for at least 6 to 8 weeks after the hemoglobin has been restored to normal levels to replenish iron stores.

Parenteral iron therapy (iron-dextran) is indicated when patients fail to respond to adequate oral dosage because of a deficiency in intestinal iron absorption. Some physicians use parenteral iron as the treatment of choice in young infants. The total amount of parenteral iron needed may be calculated as follows:

$$\frac{\text{Normal Hb.} - \text{Initial Hb.}}{100} \times \text{Blood Volume (ml.)} \times 3.4 \times 1.5$$

blood volume = 40 ml./pound of body weight
3.4 converts grams of hemoglobin to mg. of iron
1.5 provides extra iron to replace depleted tissue stores.

Injections are given daily in doses of from 50 to 100 mg. depending on age. Reticulocytes appear on the second day and reach a maximum in about five days. With both oral and parenteral iron therapy, the hemoglobin level should reach 11 gm% in approximately 3 weeks.[1] Dietary adjuvants to iron therapy are not necessary in the treatment of iron deficiency anemia.

Transfusions. This form of therapy is reserved for the infant with a hemoglobin level of about 4 gm. % or less who is debilitated from an infection, especially when signs of dysfunction are present.[1]

Anemia of the Premature Infant

These infants suffer from a biphasic anemia. The normal physiologic anemia is much more severe in these infants and is considered to be pathologic. A relatively lower initial hemoglobin mass at birth, the usual decreased synthesis of hemoglobin in the first few weeks of life, and the increased rapidity of growth and expansion of blood volume in the premature account for this phenomenon. A decreased life span in the erythrocytes of the premature has also been cited as a cause of the exaggerated drop in hemoglobin.[5]

An iron deficiency anemia will develop because of the small initial hemoglobin mass and can be prevented in these infants if one remembers that they exhaust their iron stores much earlier (in 3-4 months) than the normal child. A dosage of 35 to 40 mg. daily of elemental iron given from two months of age should protect the majority of prematures and allow for iron storage. If an anemia already exists, the dosage is increased to 60 to 90 mg. daily.

MEGALOBLASTIC ANEMIAS

These anemias are caused by a deficiency of vitamin B_{12} or folic acid which function as coenzymes in the synthesis of nucleoproteins. Ascorbic acid deficiency may occasionally cause this type of anemia by limiting the conversion of folic acid to its metabolically active form, folinic acid.

Megaloblastic anemia of Infancy

This is an acute, transitory anemia due to a deficiency of folic acid. It is precipitated by states of rapid growth, high nutritional demands, infection and prolonged diarrhea which greatly reduce the reserves of folic acid,[6] and may be influenced by many synthetic diets which are deficient in folic acid. Premature infants are especially susceptable.

Clinically, the onset is insidious and usually occurs between the ages of two and seventeen months. The usual signs of anemia are present. There may be intermittent fever, diarrhea, and hepatomegaly. The nutritional statis is poor, splenomegaly is unusual and there is no neurological component although there may be a transient histamine-fast gastric achlorhydria.[1]

Laboratory Data. Hemoglobin levels below 5 gm. % are common and the red cell count is markedly reduced. The blood smear shows a normochromic, normocytic anemia with moderate macrocytosis, hypersegmented polymorphonuclear neutrophils and thrombocytopenia. The bone marrow is diagnostic showing a megaloblastic type of erythropoiesis.

Treatment. The anemia responds to oral or parenteral folic acid given daily in a dosage of 10 to 30 mg. over a period of 2 to 3weeks. If ascorbic acid deficiency is suspected, 200 mg. should be given daily. An enriched diet containing folic acid and vitamin B_{12} is essential.

Complete recovery in a few weeks is expected, and once the hemoglobin concentration and marrow cytology have returned to normal folic acid therapy may be discontinued.

Juvenile Pernicious Anemia

This condition is extremely rare in childhood. When it does occur it has all the characteristics of the adult disease. These patients are treated identically to their adult counterparts. The only difficulty arises in the diagnosis because occasionally there is free hydrochloric acid in the gastric contents and inconsistant histamine refractory achlorhydria.[7]

HYPOPLASTIC AND APLASTIC ANEMIAS

Idiopathic Hypoplastic Anemia

This is a chronic, progressive anemia of unknown etiology which occurs most commonly during infancy and early childhood. The clinical features are due to the anemia and widespread hemosiderosis which develops following multiple transfusions. The child is healthy at birth and usually develops typical symptoms of anemia by one year of age. Pallor is usually the only significant physical finding, although hepatosplenomegaly, increased skin pigmentation, cardiomegaly, arrhythmias and refractory heart failure frequently develop secondary to transfusion hemosiderosis. In most patients the disease is chronic. The outcome may be fatal.

Laboratory Data. There is a progressive, severe, refractory. normochromic normocytic anemia with decreased reticulocytes. The white cell count and platelet count are normal. The marrow shows a striking absence of the nucleated red cell precursors with normal granulocytic and platelet series.

Treatment. Supportive *transfusions* using packed cells to maintain the hemoglobin at levels compatible with freedom from symptoms is the basic treatment. *Prednisone,* given in a daily dosage of 15 to 60 mg. depending on the age of the patient, often gives a favourable response in the marrow and pheripheral blood: erythroid hyperplasia, reticulocytosis, and increased hemoglobin and red cell levels are evident. *Intramuscular ACTH* is often beneficial in patients who are refractory to prednisone therapy. When an additional, extracorpuscular hemolytic component is suspected in the genesis of the anemia, *splenectomy* has proved effective on occasion, both in reducing the number of necessary transfusions and in restoring erythropoiesis.[3]

THE HEMOLYTIC ANEMIAS

In all hemolytic anemias, the red cell has a reduced life span. If intravascular hemolysis is present, hemoglobinemia exists, and if severe enough to excede the renal threshold (100 to 150 mg. per 100 ml), hemoglobinuria results. Due to an increased rate of pigment metabolism, these patients have a plasma bilirubin level of from 1 to 3 mg. %, associated with increased fecal and urinary urbolinogen and jaundice occurs inconsistently, depending on the functional ability of the liver to metabolise the excess pigment. The blood film shows spherocytosis, schistocytosis, macrocytosis (due to the high percentage of large immature red cells) and a reticulocytosis. These patients usually also have abnormal osmotic red cell fragility tests and a decreased red cell survival using radioactive sodium chromate for labelling the red cells.

Hereditary Spherocytosis

This is a genetically determined, chronic hemolytic disease characterized by *aplastic* crises with fever, extreme pallor, shortness of breath, nausea, vomiting and extreme weakness. It occurs chiefly among Caucasians and rarely among Negroes. The defect is transmitted as a Mendelian dominant so that males and females are equally effected.

The etiology is unknown but the basic defect consists of the production of spherocytes which, because of their shape, are trapped in the spleen and are destroyed at a more rapid rate than normal. Jaundice, accompanied by a pigmented urine (after the urine is exposed to air), symptoms referable to anemia, and splenomegaly are the important clinical features. The jaundice which may be present immediately after birth, usually disappears during infancy. An icteric tint usually becomes noticeable in the older child and becomes more pronounced in the young adult and affected parent. Gall stones occur commonly in older persons with an incidence as high as 85% of cases. Radiologically there may be thickening and striation of the frontal and parietal bones of the skull.[9]

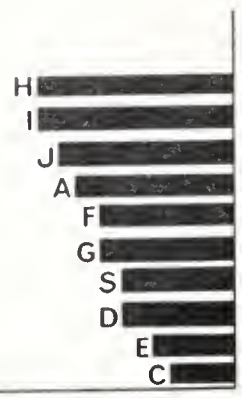
Laboratory Data. The hemoglobin usually ranges from 7 to 11 gm % and the red cell count ranges from 2.5 to 4.5 million/cu. mm. The retriculocytes range from 5 to 20%. There is increased urinary and fecal urobilinogen, spherocytosis, increased osmotic fragility and and an elevated serum bilirubin. The Coombs test is negative, and there is no abnormal hemoglobin. The bone marrow shows erythroid hyperplasia except during a crisis, at which time there is erythroid aplasia associated with reticulocytopenia, leukopenia, and thrombocytopenia. A positive family history and similar laboratory finding in affected relatives is almost essential to the diagnosis.

Treatment. Splenectomy is followed by complete and permanent relief from all signs and symptoms of the disease, although the peripheral smear remains unchanged. The operation should be executed as soon as indications of chronic illness or debility arise, except during the first year of life, at which time it is definitely hazardous. Blood transfusions are employed during the early months of life and for the treatment of a crisis with a severe anemia.

ANEMIAS AND ABNORMAL HEMOGLOBINS

The obnormal condition in these diseases is a chemical or physical change in the hemoglobin. Hemoglobin types may be determined by the use of two tests. The alkali denaturation method is used for fetal hemoglobin. Paper or starch-gel electrophoresis is used to determine other abnormal hemoglobins (figure 2).

In all body cells, the genes are paired, one member of each pair being derived from each parent. Each of the genes is called an allele. A normal person has two A alleles. The gene for any one of the abnormal hemoglobins may replace one or both genes for normal hemoglobin. When only one normal gene is replaced, the person is regarded as a carrier possessing a heterozygous hemoglobin trait. Homozygous or pure hemoglobin disease results when both genes for hemoglobin A are replaced by those of the same abnormal hemoglobin. Occasionally, both alleles may be abnormal and at



KEY
A – normal adult hemoglobin
F – fetal hemoglobin
S – sickle cell hemoglobin
other letters of the alphabet abnormal types in order of their identifieation.

Figure 2. Designation of Hemoglobin Types

The relative mobility of individual hemoglobins is represented using electrophoresis at pH 8.6.

Smith, C. H.: The Abnormal Hemoglobins: Clinical and Hematoglogic Aspects, J. Pediatrics 50:91, 1957.

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the same time dissimilar. This results in a mixed hereditary hemoglobinopathy, an example being Sickle Cell — Hemoglobin C Disease.

Sickle Cell Disease

Sickle Cell Trait. This represents the heterozygous state (hemoglobins A and S) and occurs in 7 to 9% of American negroes.[10] These persons show sicklemia when oxygen tension is lowered, but clinically are not anemic, show no physical abnormalities, and are usually asymptomatic.

Sickle Cell Anemia. This disease occurs in 0.3 to 1.3% of American negroes and the allele "S" is present in the homozygous state. The bulk of the hemoglobin (60 to 98%) is of the S variety and the remainder consists of fetal (F) hemoglobin. The basic changes are due to a combination of capillary stasis, obstruction by elongated and pointed sickle cells, thrombosis of small vessels, increased destruction of red cells, and hemosiderosis. The clinical features usually appear in the preschool age. The stasis and thrombosis in various organs are responsible for the multiplicity of symptoms. The most common complaints are joint, back, and abdominal pain, vomiting, fever, frequent respiratory infections, fatiguability and anorexia. Physical findings include marked pallor, lymphadenopathy, cardiac enlargement and splenomegaly. The spleen atrophies with advancing age due to infarction and fibrosis. The inability to concentrate urine normally is a feature of sickle cell anemia. Radiologic skeletal changes are similar to, but less marked, than those of Cooley's anemia. The blood smear shows a normochromic, normocytic anemia with various numbers of sickled cells. Reticulocytes range from 5 to 25%. The hemoglobin usually stays between 6 and 9 Gm % without transfusions. Bilirubin ranges from 1 to 3 mg. %.

Two types of crises occur in these patients. One is a symptomatic crisis with fever and severe pain in the joints, back, and extremeties, usually without exacerbation of anemia. These patients also suffer from *aplastic* crises, typical of those occuring in the hereditary hemolytic anemias.

Treatment. There is no specific treatment. Bed rest, aspirin, codeine, or other analgesics and sedatives usually suffice to control symptoms. Transfusions of packed cells are given for correction of severe anemia accompanying infection, for aplastic crises, and for relief of extreme pain when other measures fail. Splenectomy is not advocated as a routine measure. The disease is fatal in most patients before middle age, but occasionally regresses to the carrier state after adolescence.

Thalassemia (Cooley's Anemia)

The person with the trait or mild anemia as the only abnormality functions as a carrier, and is heterozygous for a gene which when homozygous produces the severe manifestations of the full blown disease. The basic genetic defect is an inability to produce adult hemoglobin and the retention of abnormal amounts of fetal hemoglobin. The patient with the severe disease has from 40 to 100% fetal hemoglobin and increased hemolysis of poorly fabricated red cells. Almost all of these patients have Mediterranean ancestry. The clinical features begin in infancy and include a characteristic faces, typical signs and symptoms of anemia, and increasing, massive splenomegaly, diminishing stature and hypogonadism as age progresses. Radiologic changes include thinning of bony cortices and trabecular atrophy, compression fractures and thickening of the skull bones with a widened diploic space (brush cut sign).[11]

The blood picture shows a microcytic, hypochromic anemia, with scattered large pale erythrocytes which contain irregulary distributed clumps of hemoglobin with the intervening areas apparently possessing staining defects.

The hemoglobin ranges between 5 and 9 gm % and the red cell count between 2.5 and 3.5 million per cu. mm. Reticulocytes range from 2 to 8%. The osmotic fragility is strikingly abnormal. Although hemolysis begins at a higher osmolarity than usual, the bulk of the red cells are markly resistant to hemolysis in hypotonic saline. The serum bilirubin usually ranges from 1.5 to 3 mg. %. Aplastic crises typical of the hemolytic anemias have been described. The red cells show a radioactive half-life of twenty five days as compared with the mean half-life of 62 days attained with normal erythrocytes.[12]

Treatment. There is no specific treatment. Transfusions

are mainly relied upon and are reserved until the hemoglobin levels drop between 6.5 and 7.5 gm.% at which point clinical symptoms usually occur. Splenectomy is indicated if transfusion requirements are progressively increased and if the spleen becomes massive and burdensome. The prognosis is poor but clinical progress is variable.

OTHER ANEMIAS

Anemia of Infection

Chronic infection is a more common cause of anemia than acute infection. Severe hemolytic anemias may occur with some infections: streptococci, staphylococci, infectous mononucleosis, Coxsackie A. The anemia associated with chronic infections probably results from a toxic depression of erythropoiesis and a decreased red cell survival time. This anemia is rarely severe and is usually normochromic, normocytic, but may be hypochromic, microcytic in nature. The reticulocyte count is normal or reduced. The bone marrow shows no hyperplasia. The serum iron is markedly lowered. Iron therapy without irradication of the infection produces no improvement. The treatment consists of elimination of the focus of infection. Iron therapy during the recovery period is frequently of value.

Erythroblastosis Fetalis

This is a very important cause of anemia in the newborn period. The student should make further reference to the study of this disease.

ACKNOWLEDGEMENT

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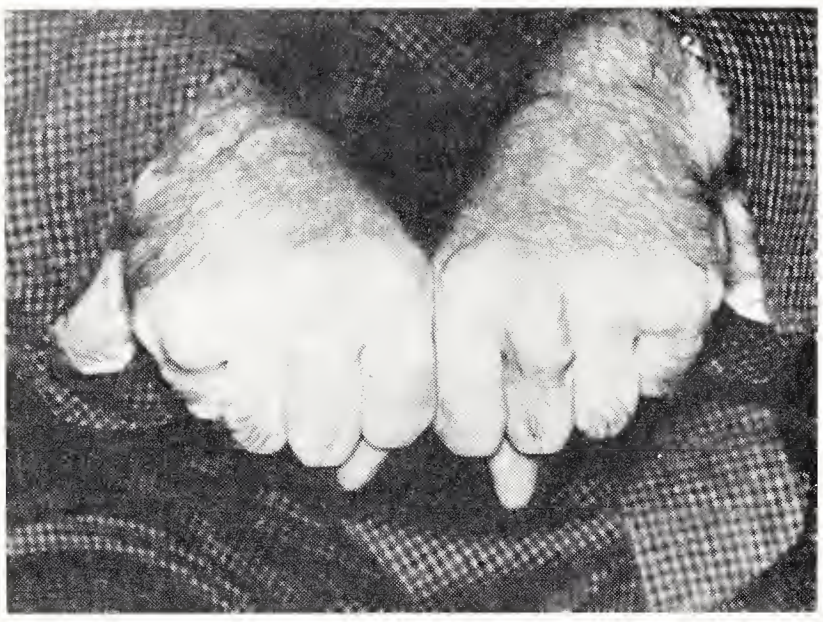

FIGURE 1: The patient is 30 years old and suffers from angina pectoris and the above pictured cutaneous nodules; serum cholesterol, 450 mg. %. Diagnosis?

FIGURE 2: What condition (or conditions) is this likely to be?

FIGURE 3: This elderly man's only complaint is painless, progressive enlargement of lumps in the neck. What is your diagnosis?

FIGURE 4: The lesion is an enlarged, solitary, non-tender, non-painful, fixed stoney hard nodule. What must the lesion be?

FIGURE 5: This man presented with a petichial rash over the chest and subconjuntival hemorrhages. What is your general differential diagnosis? How would you arrive at a more definite conclusion?

FIGURE 6: The patient complains of acute attacks of abdominal colic and ready blistering of skin on exposure to light. On examination, irregular erythematous areas of the skin are seen. Diagnosis?

See page 86 for answers

Book Review

Respiration — Physiologic Principles and Their Clinical Application; P. Rossier, A. Bühlmann, K. Weisinger; C. V. Mosby Co., St. Louis, 1960; 413 pages; 95 illustrations; $15.75.

Extensive study and investigation, particularly during the past decade, have greatly added to and altered our knowledge of respiratory physiology. The many new developments in cardiac and pulmonary surgery have been basically responsible for initiating much new interest.

This book has been written by experts experienced in the field, and is an excellent and comprehensive review of the subject, bringing the reader as up to date as it is possible to be in such a rapidly expanding field. There is no comparable text on the subject available.

The chapters dealing with normal physiology, the regulation of respiration and the clinical states of dyspnoea and cyanosis are excellent reading for students. Those parts containing detailed references to the development of formulae and equations, or extensive historical analysis may be readily by-passed.

The latter half of the book dealing with investigative methods and the clinical applications of cardio-pulmonary physiology will be of more value to the post-graduate student and clinician with an interest in the subject. For the undergraduate student much of the information will be considerably more detailed than required. It will provide, however, an excellent source of reference and a comprehensive index to the current literature should one wish precise information on any particular subject.

A condensation of the information provided in this book would make the ideal student text on the subject at the present time.

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An Approach to the Diagnosis of Leukemia

David Appert 6T3

This paper, the first of two articles on leukemia, contains a working classification and a comprehensive list of symptoms which are useful in the clinical diagnosis of this disease.

A comparatively recently recognized newcomer among the major know scourges of humanity, leukemia was first described in 1845 by two independent research workers — Bennett, a Scottish histopathologist, and Virchow, a German pathologist. Within twelve years of its recognition, the two chief varieties of chronic leukemia, as well as the acute form had been described. Since then, variations from the classic pictures have been recognized by means of ever increasing and better histologic-diagnostic technics. In addition, progressive research on the functional and dynamic aspects of the disease have added to our knowledge, and biochemical, biophysical, biological and cytological technics have supplemented our methods of understanding the disease process, its diagnosis, and palliative management.

Leukemia may be described as a generalized, purposeless, self-perpetuating, abnormal (probably neoplastic) proliferation (slow or rapid), of one of the hematopoietic tissues (bone marrow, lymphoid tissue, reticuloendothelial system, or system of plasmocytes) often associated with abnormal white blood counts and eventually leading to anemia, thrombocytopenia, and death.

CLASSIFICATION

The leukemias occur in a number of forms which differ in their clinical and hematological picture, and they can probably be best classified on this basis.

A. CLINICAL

1. *acute*: usually a sudden onset and malignant course, with a life span varying from a few weeks to usually not more than twelve months, the median survival being seven months from the appearance of the first symptom.
2. *chronic*: usually a slow onset and rather benign course, with a life span from more than twelve months to perhaps twenty years, the median survival being approximately forty-two months from the onset of symptoms.

B. HEMATOLOGIC

1. Degree of cell differentiation
   a. "*immature*": little, if any, apparent tendency to differentiation or maturity with large numbers of primitive ('blast) cells, often many mitotic figures.
   b. "*mature*": well-defined differentiation to mature types of cells, and a rather slow accumulation of the proliferating cells in various tissues.
2. Cell lineage
   a. *stem-cell* (i.e. lineage not identifiable)
   b. *granulocytic*
   c. *lymphocytic*
   d. *monocytic*
   e. *plasmocytic*
3. Peripheral white blood cell count
   a. *leukemic*: high leukocyte counts.
   b. *subleukemic*: normal or low normal leukocyte counts but with abnormal differential counts showing primitive leukocytes.
   c. *aleukemic*: low leukocyte counts with no abnormal or primitive cells in the blood smear.

Theoretically, it should be possible to observe acute and chronic granulocytic, lymphocytic, monocytic and plasmoctyic leukemias. However, chronic monocytic leukemia is rare, perhaps non-existant, and acute plasmocytic leukemia has not been described. The common acute entities encountered are the stem-cell, granulocytic, lymphocytic and monocytic types; the common chronic leukemias found are the granulocytic, lymphocytic and plasmocytic types.

PATHOGENETIC SYMPTOMATOLOGY

Initially leukemia has no specific clinical manifestations of its own. Symptoms arise only when the pathologic process is sufficiently advanced to cause: A. interference with the proper production or maintenance of the normal blood cells resulting in abnormal hematologic states; B. obvious changes in the blood-forming or lymphatic organs, as well as interference with the activity of other essential organs, both the consequence of the presence of tumor tissue; C. profound alteration in the metabolism of the body with a hypermetabolic state.

Abnormal Hematologic States

It should be emphasized from the beginning that the most abrupt symptoms arise when there are ad-

vanced changes in the normal complement of the blood cells.

Many cases of leukemia have their onset in the guise of an infectious process, and their diagnoses follow in the wake of an incomplete recovery perhaps punctuated with several relapses. An actual or "functional" *granulocytopenia* predisposes to ulcerating infections of various types, often due to uncommon organisms such as Candida Albicans or other fungi, and the site of predilection seems to be the mucus membranes, particularly of the oral-pharyngeal cavity.

Leukemic destruction of the megakaryocytes leads to *thrombocytopenia* with subsequent bleeding from the body orifices and into the body organs and cavities, as well as cutaneous hemorrhanges ranging from petechiae to large ecchymoses. Purpura is the commonest hemorrhagic manifestation followed by epistaxis, bleeding from gums, hemoptysis, melena, menorrhagia, conjunctival and retinal hemorrhages, hematemesis, and hematuria in that order. Contributing to this hemorrhagic state are such factors as: trauma, either surgical or accidental; interference with thrombin-fibrinogen reaction; and abnormalities of small blood vessels due to protein or secondary amyloid deposition.

It is to be noted that the granulocytopenia and thrombocytopenia are much commoner in the acute leukemias than in the chronic, and possibly much commoner in children than in adults with acute leukemia.

Sooner or later every leukemic patient develops *anemia,* with its concomitant symptoms including general fatigue, lassitude, dizziness, dimness of vision, headache and paresthesiae. The possible mechanisms of this anemia include: physical displacement of marrow erythroblasts by rapidly proliferating leukemic leukocytes; metabolic uptake by leukemic cells of essential materials for erythropoiesis; hemolysis of mature red cells on the basis of auto-immunity or hypersplenism; hemorrhage as a result of clotting abnormalities or defects.

Various *dysproteinemias* occasionally occur. Hypogamma-globulinemia, seen mainly in chronic lymphocytic leukemia, tends to increase the danger of infectious complications, especially in the rare cases of agammaglobulinemia. Hyperglobulinemia (macro- and cryo-), found mainly in plasmocytic leukemia, may increase the incidence or severity of hemorrhagic manifestations.

The excessive leukemic cell turnover with its increased purine metabolism leads to a state of elevated *uric acid* concentrations in both serum and urine. Crystallization of the uric acid may precipitate attacks of acute gout, either widespread systemically, or locally in the kidney with calculus formation and tubular obstruction.

As a result of high leukocyte phosphorus content the blood *phosphorus* is elevated. Blood cholesterol may be normal or reduced; the total *lipids* and fatty acids of the whole blood, serum and plasma have been found to be greatly elevated. Abnormally elevated plasma *lactic dehydrogenase* concentrations have been reported in acute and chronic granulocytic leukemia but not in chronic lymphocytic leukemia.

Presence of Tumor Masses

Local symptoms and signs may be referable to the blood-forming or lymphatic organs, or to other organ systems.

The commonest tumor masses found are *enlarged lymph nodes* of varying degrees and distributions. The nodes are usually smooth, firm, of variable size, and painless unless secondarily infected. They give rise to their symptoms by one of two basic pictures — either disfigurement of superficial tissues, or pressure symptoms because of encroachment on the trachea, bronchi, esophagus, bladder or rectum. Chronic lymphocytic leukemia frequently exists unnoticed until one or more of the cervical or axillary nodes become enlarged. In chronic granulocytic leukemia, lymphadenopathy is unusual, except in some cases at the late stages; lymphadenopathy is usually of minor degree in acute leukemias.

Complaints stemming from an *enlarged spleen* are rather frequent in chronic granulocytic leukemia, but almost unknown in the other forms. Splenomegaly may present as a lump in the abdomen, a dragging sensation when upright, a postprandial sense of fulness, or subcostal pain following ischemic infarction with perisplenitis. However, the degree of splenomegaly does not appear to be related to the total number of leukocytes.

Practically a constant accompaniment of splenomegaly is *hepatomegaly*. But the liver is seldom greatly enlarged and is usually painless and non-tender.

With the exception of the acute leukemias in adults where they may be less prominent, the liver, spleen, and lymph nodes are nevertheless involved in the great majority of cases. However, they are usually the presenting complaints in the chronic leukemias and are certainly less marked in acute leukemias.

Marked *bone marrow* involvement is practically constant in leukemia at some stage of the disease. It is responsible for not only hematologic abnormalities, but also local pain and tenderness, especially over the sternum in acute childhood leukemia.

While involvement of the bone marrow, liver, spleen and lymph nodes brings about by far the commonest clinical manifestations of leukemia, autopsy findings show that the disease affects many other organ systems, even though symptoms pointing to such an invasion may be completely lacking.

Involvement of the *bone and joints* is common in children and often leads to pain in these areas. Because of the sometimes associated local or general swelling or the flitting nature of the pain, it is often misdiagnosed or rheumatic fever. Local joint pain results from stretching of the soft synovial tissue either from direct membrane invasion or bony involvement near the insertions of the joint capsules; local bone pain arises when the bone is encroached upon centrally from an expanding marrow cavity or when subperiosteal deposits occur.

Both central and peripheral *nervous system* involvement is known. Cerebral complications, including meningeal signs, stroke syndromes, isolated paralysis or cranial nerve palsies, result from multiple areas of infarction or massive hemorrhage into the cerebrum or subarachnoid space, usually in association with the presence of leukemic nodules. Leukemic infiltrations within the arachnoid and Virchow-Robin spaces will produce a meningeal leukemia with the symptoms and signs of increased intracranial pressure, cranial nerve palsies, and focal cortical symptoms if dural infiltrations exist alone. Spinal cord lesions result from epidural leukemic infiltrations with secondary root and cord compression syndromes. Peripheral neuropathies may be due to infiltrations of peripheral nerve sheaths.

Oral-pharyngeal involvement may be due to hemorrhagic tendencies and is frequently due to superimposed infections, almost 50% being due to monilia in children with acute leukemia. However, there may also be infiltrates producing gingival hypertrophy, characteristic of monocytic leukemia, or tonsillar enlargement, frequent and early in chronic lymphocytic leukemia.

Dull pain or indigestion in *gastric* involvement, and diarrhea in *intestinal* involvement are the usual mild and non-specific symptoms indicating leukemic proliferation in this system. The signs and symptoms of ulceration, perforation or obstruction may occur. However, there is little relationship between the anatomical extent of the process and the clinical symptoms met with.

Skin lesions manifest either as leukemic lesions which are specific for leukemia and made up of leukemic cells, or as leukemids which are non-specific lesions encompassing vesicles, pustules, wheals, bullae, petechiae, hematomas, papules, nodules, exfoliative dermatitis and herpes zoster. Skin involvement is frequently heralded or followed by pruritis, and is most common in chronic lymphocytic leukemia.

Cardiac infiltration is a frequent autopsy finding but rarely manifested clinically. The most likely effect of leukemic infiltration would be myocardial foci producing bundle branch block with subsequent heart failure or pericardial infiltration with pericarditis.

Respiratory involvement may show invasion, whether isolated, confluent or miliary, into the lung parenchyma. However, when respiratory symptoms occur they are usually due to pressure symptoms from encroachment on the trachea or bronchi by enlarged lymph nodes. As well, leukemic pleural lesions may produce effusions.

Despite the *renal* lesions associated with uric acid calculi, there is no evidence that leukemic infiltration alone leads to impairment of renal function irrespective of an usual diffuse renal infiltration by leukemic cells.

Hypermetabolism

Leukemia, being a probable neoplastic process, produces a hypermetabolic state resembling that of hyperthyroidism (however, the characteristic nervousness, irritability, insomnia, and tremor of hyperthyroidism are usually lacking). General symptoms of this hypermetablic state include:

1. lack of energy; weakness; fatigue
2. malaise
3. anorexia
4. loss of weight; cachexia
5. fever; night sweats; hot flushes

The general symptoms may appear relatively rapidly but more often are so gradual in their development that many weeks or months may pass before the patient realizes that his health has been deteriorating; often they are not mentioned at all until a physician inquires specifically for them at a time when other symptoms or signs may have become apparent.

LABORATORY INVESTIGATION

In many cases the patient's history and physical signs may arouse suspicion of the diagnosis of leukemia, but it is never possible to obtain proof without recourse to laboratory examination. Unfortunately, space does not permit a detailed description of the various laboratory findings; only an indication of these data can be offered in this article.

Examination of the Blood

The presence of abnormal leukocytes with or without leukocytosis, thrombocytopenia, and anemia are

the features on which the diagnosis of all types of leukemia must eventually rest. These occur in very varying combinations, with cases of acute leukemia tending to show more severe anemia and thrombocytopenia, lower leukocyte counts and more primitive cells in the blood stream, while those with chronic leukemia are more likely to have higher leukocyte counts with mature or moderately immature cells predominating.

Examination of the Bone Marrow

The most important diagnostic feature in bone marrow examination is the discovery of the type specific abnormal cells in the various leukemias. In most cases the films will be of a uniformly high cellularity, but sometimes the hyperplasia is patchy and is found in some solid fragments but not in others. Also, instances of reduced marrow cellularity may occur giving rise to the so-called "aplastic" leukemia. In general, a marrow count of at least 20 per cent or more of 'blasts is indicative of leukemia. At the same time a usual diminution in the percentage of erythrocyte precursors and of megakaryocytes may be found; however, this is by no means constant and they may on the contrary show an increase.

It should be emphasized that leukemia is not a "blood disease" *per se,* for the blood picture is only a reflection of the balance existing between the rapidity or paucity of proliferation and exfoliation of cells of the blood-producing tissues, the speed at which the new cell dies, as well as the avidity of the outlying tissues for absorption and destruction of the circulating blood cells. Because of this dynamic status, the blood is sometimes an imperfect reflection of the underlying pathology and physiology. Bone marrow aspiration should be reserved only for those cases where a peripheral smear in conjunction with clinical signs and symptoms, does not give a clearly positive diagnosis.

CONCLUSIONS

Like other neoplastic proliferations, leukemia is subject to considerable variations in its rate of growth, and morbidity therefore ranges from a very acute disorder of but a few weeks duration to a very chronic one compatible with life for even many years. Some leukemias are relatively benign but tend to become more malignant with time; transition from one type to another may be observed. The course depends upon the type of cell that is proliferating, its rapidity and extent of proliferation, and upon such therapeutic measures as transfusions, antibiotics, steroids and chemotherapeutic agents. It is impossible to predict how acute or chronic a leukemia will be. In any case, all leukemias are ultimately fatal.

The study and understanding of leukemia is one of tremendous magnitude. It is hoped that the reader has learned a basic, comprehensive, and unsophisticated approach to the clinical and laboratory classification and diagnosis of leukemia. No attempt to discuss the etiology, incidence, differential points from the leukosarcomas or other myeloproliferative disorders. or treatment of leukemia has been made. The reader should pursue further reading along all these lines.

ACKNOWLEDGEMENT

The author wishes to sincerely thank Dr J. Crookston, Toronto General Hospital, for his helpful suggestions in the preparation of this article.

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Treatment of the Leukemias

Mary Jane Ashley 6T3

As a sequel to the preceding article, this paper deals with the general treatment for all leukemias and specific treatment which depends on the cell-type of the leukemia.

Although leukemia is still a fatal disease for which no cure exists, modern methods of treatment have resulted in a marked reduction in morbidity and in some cases a prolongation of life. Careful and judicious clinical management can ameliorate many of the symptoms of leukemia, while minimizing hospitalization, inconvenience and expense, and allowing the patient to lead a fairly normal existence for a good part of his remaining life.

Certain responsibilities accompany the diagnosis of leukemia. The physician must be convinced beyond any doubt that the diagnosis is correct. He is then faced with the problem of telling the patient at least part of the truth of his disease. At the same time he must inform at least one responsible member of the patient's family of the whole truth. The natural reaction to such a revelation is firstly one of dismay, followed by disbelief, and then the desire to disprove by further investigation and consultation the ominious diagnosis. The physician should be willing to assist the family in gaining other competent medical opinion if this is desired.

The psychological problems facing a patient suffering from an incurable disease are not to be underestimated. Each case must be judged on its individual merits. The amount of information given the patient will depend on his character and maturity. Perhaps it is best to reveal the facts gradually and gently, to answer questions asked honestly but not necessarily completely, to dispel fears as best as possible, and always to keep hope alive as one of the most valuable therapeutic measures available both for the patient and the family. Certainly the physician must be a constant support to both family and patient, always mindful of normal emotional reaction to a fatal disease.

The Aims of Therapy

The specific aim in the treatment of leukemia is the control of the leukemic process in the blood, bone marrow, and tissues, by the use of certain specific antileukemic agents, with the ultimate idea of inducing a partial or even complete remission. Such measures as external and internal irradiation, and chemotherapy, including the use of antimetabolites, cytotoxic substances and the adrenocortical hormones will be considered under specific agents. Certain general measures are also crucial to the adequate management of the leukemic patient. The prevention and control of hemorrhage, the relief of anemia, the control of infections and the use of antibiotics, and the maintenance of weight, appetite and general well-being will be considered under general measures.

GENERAL MEASURES

Hemorrhage

Hemorrhage in leukemia is usually the result of thrombocytopenia which may be part of the disease process or may result from therapy. If the latter is the case, then therapy must be interrupted and re-evaluated. If thrombocytopenia is the result of the disease process, then control of the leukemia by a suitable chemotherapeutic agent may result in return of the platelet count to normal. In the meantime hemorrhage must be controlled by local measures, such as direct pressure packs for epistaxis, and the local application of thrombin. If severe bleeding occurs, fresh whole blood which is rich in platelets, should be given.

Blood transfusions are usually considered as a purely supportive measure, but there is some evidence to show that in the acute leukemias some anti-leukemic effect may result as well.

Anemia

The most important factor in controlling anemia in any form of leukemia is the effective treatment of the underlying leukemic process. When this is successful, erythropoiesis improves, the platelet count returns to normal and the hemoglobin rises. This is particularly true in acute lymphoblastic and chronic myelocytic leukemia. In acute myeloblastic leukemia, improvement may be delayed or may not occur and blood may have to be used to improve the anemia. In chronic lymphocytic leukemia anemia is one of the later developments and is not greatly influenced by therapy, so that it is

not uncommon for anemia to persist even after achieving satisfactory control of the lymphocytic proliferation. In such cases a trial of prednisone in low or moderate dosage (10-20 mg. daily) is often worthwhile. If the anemia is hemolytic and especially if there is a positive antiglobulin test (Coomb's Test), remarkable improvement is seen. Even when the anemia is not clearly hemolytic some rise in the hemoglobin level occurs. Concomitant administration of anabolic hormones may further the antianemic effect while minimizing osteoporosis. With the use of steroids special attention to the increased hazard of infection, which is often undetected and may become quite severe, is important.

Blood should be used sparingly in the early stages of the disease and should be kept in reserve for later treatment. Usually blood is not necessary unless the hemoglobin is less than 10 grams %. In cases of frank hemorrhage blood should be given to combat shock, and in refractory thrombocytopenia fresh whole blood rich in platelets is needed. Post-transfusion complications are always a risk.

Infections and Antibiotics

Infections are a major problem in leukemia, especially in the acute leukemias and chronic lymphocytic leukemia. The most satisfactory reduction in susceptibility can be achieved by inducing a remission of the leukemic process, but when this is impossible or has not yet been achieved, the prompt use of appropriate antibiotics can prevent minor infections from becoming serious and widespread. It has not been shown that the use of prophylactic antibiotics is helpful. This may indeed be harmful by allowing drug-resistant organisms to develop in the normal flora. An attempt to identify the causative organism should be made before drugs are started. Wherever possible bacteriocidal rather than bacteriostatic agents should be used. While antibiotics improve survival and decrease morbidity, there is no evidence that they play any significant part in inducing remissions of the leukemic process.

The skin, urinary tract and respiratory tract are favorite sites for infection. Common organisms cultured are *Streptococcus viridans, Pseudomonas,* and the coliforms. In acute leukemia, particular care of the mouth is especially important. Bleeding from the mucous membranes occurs easily. A soft toothbrush should be used, and the mouth should be washed with a mild antiseptic after each meal. A special watch should be kept for fungal infections of the mouth, such as candidiasis, since these are relatively common in patients treated with cytotoxic drugs and steriods for a number of weeks. Local treatment with Nystatin is usually effective in preventing dangerous spread.

The most common condition giving rise to infection in chronic lymphocytic leukemia is the presence of hypogammaglobulinemia or even agammaglobulinemia. As in other lymphoproliferative disorders, once this complication develops, it is usually permanent. Infection in this instance is treated with appropriate antibiotics and a course of gammaglobulin injections.

Appetite, Weight and Sense of Well-Being.

Although no specific dietary measures are indicated in the treatment of the leukemic patient, the diet should be as well balanced and appetizing as possible. Appetite usually improves with control of the leukemic process and the weight increases accordingly. There is no indication that activity is harmful and hemorrhage occurs as frequently in the quiet as in the active case. From the psychological standpoint activity should be encouraged and the patient should be kept ambulatory and engaged in his normal activity as long as possible. Sedation and analgesics may be needed in the terminal stages.

Other Complications

Anuria. As the result of rapid tissue breakdown especially after the institution of therapy, a hyperuricemia may occur and crystallization of uric acid in the renal tubules and ureters may result. Sodium bicarbonate and large quantities of fluid reduce the likelihood of oliguria or anuria occuring. The physician must be aware of the possibility of this complication and immediate ureteral catheterization and irrigation should be undertaken if anuria occurs. This is dangerous if a bleeding tendancy is present. The artificial kidney has been used successfully in the circumstances.

Leukemic infiltration of the kidneys is uncommon and so not likely the cause of renal complications. Infiltration is treated with irradiation if it does occur. Uric acid crystallization and urinary tract infections are the major causes of urinary tract complications. They must be carefully watched for and treated with appropriate therapy immediately.

Leukemic tumour masses. The treatment of this complication is discussed under irradiation.

Intracranial complications. Signs and symptons of increasing intracranial pressure, meningeal irritation, seizures, and cranial nerve palsies may be seen in acute leukemias even after the hematological picture is one of remission. Amethopterin intrathecally in doses of 0.1-0.5 mg. per kilogram may be repeated once or twice at three to four day intervals to achieve regression of the tumour.

SPECIFIC MEASURES

Unlike the general measures which apply to the treatment of all forms of leukemia, the specific measures employed vary with the cell type of leukemia involved and the clinical picture present. The correct choice of a suitable therapeutic agent for the process encountered will appreciably affect the success of therapy. It should be remembered that wherever possible the patient should be ambulatory rather than hospitalized for financial and psychological reasons. The cost of therapeutic agents must be considered in relation to their possible clinical effect, bearing in mind the tremendous financial burden which a long illness may bring upon a family. Wherever possible only one agent should be employed at a time, so that if toxic side-effects do arise, there will be no confusion as to their source, and like-wise if resistance develops it is to one agent at a time only, others still being available.

Irradiation

X-Rays. Irradiation may aggravate rather than ameliorate the acute leukemic state. Its usefulness is therefore confined to the chronic leukemias. An increased leukocyte count is not alone an indication for irradiation but should be accompanied by a decline in the clinical state, with such symptoms as loss of weight, increasing pallor, pressure symptoms, unsightly and uncomfortable glandular enlargement, pain as the result of tissue invasion, and symptoms as the result of increasing anaemia. Irradiation is more useful in the treatment of chronic myelocytic leukemia, where indications are more common, than in the treatment of chronic lymphocytic leukemia. However, when indications are present, chronic lymphocytic leukemia is much more sensitive to irradiation than chronic myelocytic leukemia and responds to much lower doses. Irradiation may result in the relief of pain, a decrease in the anemia with a return of the platelet count to normal, a reduction in hepatosplenomegaly, a decrease in size of large tumours and lymph nodes with the resulting relief of pressure symptoms, a gain of weight, strength, and general well-being, a decrease in the leukocyte count and a reduction of immature forms in the peripheral blood stream.

Toxic symptoms necessitating cessation of irradiation include rapid loss of weight, anorexia, nausea, vomiting, diarrhea, increasing anemia, and immature leukocytes, and the onset of bleeding with thrombocytopenia.

Irradiation of the spleen with repeated daily doses through different areas of skin to avoid radionecrosis until the leukocyte count falls to around 20,000 per cu. mm. is the most commonly used method. Treatment is then stopped since a further fall in leukocyte count usually takes place during the next few days. Satisfactory clinical and hematological control can be achieved by repeating courses of treatment whenever the leukocyte count rises above 50,000 or when splenomegaly or other trouble symptoms recur. Periods of complete or partial remission may last for a few weeks to many months, but the period of remission after each successive treatment course tends to get shorter and a refractory state eventually develops.

Radioactive phosphorus (P^{32}) can produce periods of remission. It is used in chronic myelocytic leukemia only, and then rarely. In doses normally employed it can cause severe bone marrow depression.

Chemotherapy in the Chronic Leukemias

Busulfan (*Myleran*). Busulfan has been widely accepted as the drug of choice in the management of chronic myelocytic leukemia. An alkylating agent, its cytotoxic effect is brought about by the action of its reactive alkyl groups which attach to DNA molecules thereby changing the nature of the genetic material of the cell. This effect of busulfan unlike the nitrogen mustards is limited essentially to the granulocyte series of cells in the bone marrow, the gastro-intestinal and lymphoid germinal follicles not being appreciably damaged. This selective inhibition of the bone marrow with minimal effects on other tissues makes this drug singularly free from side-effects, especially those arising from toxic action on the gastro-intestinal cells causing severe nausea and vomiting which occurs with the nitrogen mustards and some other cytotoxic drugs. The chief danger is the development of pancytopenia secondary to severe bone marrow depression. This may occur if treatment is prolonged beyond the recommended time or with a normal course of therapy in an unexpectedly sensitive individual. The warning signal of pancytopenia is the development of thrombocytopenia.

Busulfan is simple to administer, being effective when given by mouth usually in a single daily dose of 4-6 mg. before breakfast. Almost all patients respond initially to it, with gradual symptomatic improvement and reduction in splenomegaly accompanying the fall in leukocyte level and subsequent rise in hemoglobin and red cell count. Treatment is usually continued until the leukocyte count has fallen to about 10,000 per cu. mm. Therapy is then discontinued until the clinical state begins to deteriorate. Therapy is then repeated. After subsequent courses the period of remission tends to become shorter and in the end about

one half the patients enter a phase of acute myeloblastic leukemia.

In comparison to radiotherapy, busulfan has the advantage of requiring no elaborate apparatus, being convenient for the patient, easy to administer, and so well suited for the treatment of the patient in an ambulatory state. The chance of toxic effects is certainly no greater than with radiotherapy so that it is now usual to prescribe busulfan in preference to radiation, except where there are specific indications for radiation.

Chlorambucil (*Leukeran*). This alkylating agent is the drug of choice in the treatment of chronic lymphocytic leukemia. It too is orally administered in daily doses of 0.2 mgs. per kilogram. The length of treatment should be adjusted according to the lymphocyte count and the clinical picture. Usually 70-90 days of therapy are required. Its activity is directed chiefly against lymphocytic proliferation and when used systemically it is often successful in reducing the size of lymph nodes and spleen as well as reducing the lymphocyte count. The chief toxic effect of chlorambucil is bone marrow hypoplasia, although dermititis and jaundice have been reported as well.

TEM (*Triethylenemelamine*). Another member of the nitrogen mustard group of drugs, TEM is used only in the treatment of chronic lymphocytic leukemia. It does not have the margin of safety that chlorambucil has, the margin between therapeutic and toxic dose being quite slim.

Thio-TEPA. About as useful as TEM being used only where resistance develops to the drug of choice, this drug must be given intravenously and so administration is awkward.

Urethane. If resistance develops to busulfan, urethane can be used in the treatment of chronic myelocytic leukemia. It does not have as much effect on masses as busulfan and its toxic effects chiefly involving the gastrointestinal tract are greater.

Chemotherapy in the Acute Leukemias

Purine Analogues — 6-Mercaptopurine. This drug is the most effective member of the group of drugs known as the purine analogues. It is an antagonist of adenine and hypoxanthine which it closely resembles, and so acts as an antimetabolite in the early stages of nucleic acid synthesis in the body and influences neoplastic cell metabolism selectively without causing severe damage to normal cells. It is effective in all forms of acute leukemia. It is effective in children who have become resistant to folic acid antagonists, the treatment of choice in children, and also in those who have become resistant to steroids. It is much more effective in adults with acute leukemia than the folic acid antagonists.

The usual dosage is 2.5 mg. per kilogram given orally in a single dose, which is usually continued throughout a remission until signs of relapse occur or toxic symptoms are found. The main toxic effect is suppression of the bone marrow with pancytopenia. Liver damage with the development of jaundice may also occur, as can redness and ulceration of the buccal mucosa, lips and tongue. Once resistance to this drug develops, resistance is also present to other members of the purine analogue group.

Folic Acid Antagonists — Amethopterin (*Methotrexate*). The close similarity between members of this group of chemicals and folic acid makes it very probable that the folic acid antagonists act as specific antimetabolites of folic acid, causing a block in the transformation of folic acid to folinic acid which is an essential vitamin to the normal growth and division of the cell. Although these drugs are relatively ineffective in adults, they are capable of producing some degree of remission in forty to seventy percent of the acute leukemias of childhood. Monocytic leukemia is often refractory but acute lymphoblastic and myeloblastic as well as stem cell leukemia are often amenable to treatment with folic acid antagonists. The average length of remission produced is about eight months.

Amethopterin is the drug usually employed because dose regulation is more readily achieved, but aminopterin is an equally effective agent. The dose of amethopterin for children 2-8 years old is 2.5-5 mg. per day, and this is given until response is seen or until signs of toxicity including stomatitis, diarrhea, skin and mucous membrane hemorrhage, pancytopenia and alopecia occur. Resistance begins to develop after the first course of therapy and another agent must be resorted to before long.

The intrathecal use of amethopterin has been discussed.

Adrenocortical Hormones and ACTH.

These hormones in exerting a lympholytic effect are used with excellent response in the acute leukemias of childhood and in acute lymphoblastic leukemias in adults. They are contraindicated in acute myeloblastic leukemia in adults. Although not used as a specific measure in acute myeloblastic leukemia, they are sometimes used as a supportive measure in hemorrhagic complications.

OBSERVATIONS DURING THERAPY

It is necessary to follow the course of the patient

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Profiles

Dr. A. L. Chute

For many people, the decision to study medicine is based on a multitude of factors, and is reached only after much thought, inquiry and self-examination. Dr. Chute was more fortunate. For him, it was never a question of whether to go into medicine, but simply when? He was born in India in 1909. His father was a missionary, his mother a practicing physician, and he was surrounded by the doctor's life from his earliest years. At the age of ten he returned to Canada, and continued his education in Toronto.

During his undergraduate days at University of Toronto, he came into contact with the vivid and dynamic teaching of Dr. Best. This experience was never forgotten. He took his B.A. and M.A. by 1932, went into the second medical year and graduated with honours in 1935. After a junior internship at the TGH, he returned to physiology for a year at the Hospital for Sick Children. It was to be a temporary measure, because he intended to go into general practice, but he subsequently accepted a Belt Memorial Research Fellowship at University College in London. He took his Ph.D. in Physiology there, two years later.

Dr. Chute had barely come back as a clinical assistant at the HSC when war broke out. He served five years with the Canadian Army Medical Corps as the leader and physiologist of a team of specialists who studied shock and infection and their correlation with various types of wounds. Much of this was pioneer research, and he was awarded the O.B.E. in 1943 for his part in this work. After the war, he spent a year at the New England Deaconess Hospital in Boston, working on diabetes. After this he then accepted the post of Associate Professor in the Department of Banting and Best Medical Research. Since 1951, he has been Chief of Paediatrics at the Hospital for Sick Children and a part time Professor in the Department of Banting and Best. He is presently a councillor of both the Canadian College of Physicians and Surgeons and of the Medical Research Council, and is a member of many scientific societies. He is married, has two children, and spends much of his spare time with his family at a summer cottage where he practices his hobby of carpentry.

In addition to his administrative and research work, Dr. Chute is vitally interested in education, both in the very broad sense and in its application at the medical undergraduate level. For those intending to continue in academic work, he stresses the need for good experience in some highly specialized field, above and beyond the normal curricular content of any course. Ideally, this should be a natural process where the student follows up those questions and problems which interest him. Hence even prior to university, the system of education should have yielded students who have a basic interest in what they do, coupled with a frank curiosity and the energy with which to satisfy it. Dr. Chute himself is just such a man, and both our faculty and the field of paediatrics have profited.

Jarda Polak 6T4

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undergoing radiation or chemotherapy with careful and repeated clinical and haematological examinations. Hemoglobin, white cell count, platelet count and blood smear should be done frequently. Changes in the size of the liver, spleen, and lymph nodes, as well as of weight, sense of well-being and appetite should be noted. The manifestations of hemorrhagic tendencies, fever, and bone tenderness are important observations in the clinical evaluation of the patient. Examination of the bone marrow may occasionally be a helpful supplement to the peripheral blood findings, but this procedure is unpleasant to the patient and should be kept at a minimum.

ACKNOWLEDGMENT

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Pancytopenia

Joy Armstrong 6T3

Disorders of the marrow and spleen which cause pancytopenia are discussed and principles of treatment are outlined.

Pancytopenia implies a reduction in the number of each of the three formed elements of the blood; and for practical purposes it exists when there is an erythrocytopenia, less than 4,000,000 RBCs per cu. mm., a leucopenia. less than 5,000 WBCs per cu. mm. and a thrombocytopenia, less than 200,000 per cu. mm. A number of disorders are commonly associated with a pancytopenia, and will be dealt with individually. A pancytopenia, occurs very rarely with equine infectious anemia, pregnancy, sclerosis of the thyroid gland, Simmond's disease, thymic tumours and ingestion of infected grain.

The clinical signs and symptoms of pancytopenia are variable and depend upon the degree of anemia, leucopenia and thrombocytopenia. Anemia may cause fatigue, pallor, dyspnoea on exertion and pyrexia; leucopenia may cause recurrent infections; and thrombocytopenia may cause bleeding, easy bruising and petechiae.

PANCYTOPENIC DISORDERS

Marrow Depression

Bone marrow depression (aplastic anemia) is much in the public eye at the moment due to the publicity given to the cases associated with chloramphenicol. In most cases of aplastic anemia however, no offending agent is discovered. Immunological factors are postulated as a means of destruction of marrow cells but they have not been demonstrated. Hereditary factors are important in some cases: in familial aplastic anemia or Fanconi's anemia, pancytopenia occurs along with pigmentation, abnormal thumbs, dwarfism, microcephaly, hypogenitalism, strabismus, microphthalmia, kidney abnormalities and mental retardation.

Physical and chemical agents form the second largest etiological group and are listed in Table 1. The high risk agents regularly produce aplasia if sufficient doses are given. The low risk agents only occasionally produce aplasia and may depend on an idiosyncrasy for their effect.

Some drugs used in the treatment of leukemia inhibit cell division at a specific stage of mitosis and have a marked effect on the rapidly dividing cells of the bone marrow. Early effects include lymphoid hypoplasia and decreased anti-body formation. Later effects include leucopenia, thrombocytopenia and finally erythrocytopenia. Very little is known of the mechanism behind the effects produced by other drugs.

Large doses of radiation over a short period of time cause an initial increase in neutrophils but in one week a marked lymphopenia ensues, followed by pancytopenia. Smaller doses given over a longer period of time cause a gradual decrease in neutrophils and platelets over 2-5 weeks. The erythrocytopenia is delayed because of the longer life span of the red blood cell as compared to that of the white blood cell.

Clinically, the course of aplastic anemia may be acute and fulminating with uncontrollable hemorrhage and overwhelming sepsis, or it may be chronic and prolonged, with anemia the most serious complication requiring repeated transfusions to maintain the hemoglobin level. Splenomegaly or hepatomegaly may be present, but rarely lymphadenopathy, unless infection is also present. The peripheral blood smear shows a normocytic, normochromic anemia, thrombocytopenia, and leucopenia with a decrease in granulocytes. The bone marrow is hypocellular and fatty with normoblastic erythropoiesis. It shows a relative increase in lymphocytes, plasma cells and reticulum cells. A hypercellular bone marrow is reported to have occurred in aplastic anemia but this could conceivably result from a folic acid deficiency or a maturation defect.

Marrow Destruction

Myelophthisic anemia is a synonym for the destruction or replacement of bone marrow. It may be caused by metastasizing carcinomas, lymphomas, leukemias, multiple myeloma, myelosclerosis, tuberculosis, sarcoidosis and Gaucher's disease. In addition to the pancytopenia which may be present, a leukoerythroblastic blood smear is usually seen.

The most common carcinomas to metastasize to the bone marrow are breast, prostate, and lung. Marrow aspiration at the site of bone tenderness usually yields the tumour tissue. Serum acid and alkaline phosphatases may be helpful.

Malignant lymphomas, such as Hodgkin's disease, lymphosarcoma and reticulum cell sarcoma present

High Risk	Moderate Risk	Low Risk
ionizing radiation nitrogen mustards, urethane, myleran, anti-metabolites benzene	chloramphenicol mesantoin gold preparations trinitrotoluene (TNT), arsenobenzols	streptomycin, sulfonamides, tetracyclines chlorpromazine, meprobamate phenylbutazone, pyribenzamine quinacrine, carbimazole, tridone chlorophenothane (DDT), dinitrophenol carbon tetrachloride, hair dyes bismuth, mercury, colloidal silver, inorganic arsenicals

Table I.
Physical and Chemical Agents Associated with Bone Marrow Depression
Adapted from Bloom, A. L., in The Practitioner, Feb., 1962.

with fever, sweats, malaise, pruritis, localized or generalized lymphadenopathy or hepatosplenomegaly. The diagnosis is made on surgical biopsy of the bone marrow or the lymph nodes.

Multiple myeloma rarely presents with a pancytopenia or a leukoerythroblastic anemia. The anemia is usually normocytic with a variable leucocyte picture. The marrow shows increased plasma cells in varying degrees of maturity. Abnormal serum proteins and osteolytic lesions in bone may provide important clues to the diagnosis.

Myelosclerosis, a disease in which the bone marrow is replaced with fibrous tissue, usually presents with a leukoerythroblastic peripheral smear and hepatosplenomegaly. The degree of fibrosis or cellularity of the marrow does not correlate with the severity of the myeloid metaplasia as measured by the size of the liver and spleen and the microscopic estimate of splenic and hepatic hematopoiesis. A surgical or trephine biopsy of the marrow is usually necessary for diagnosis, since sternal puncture is rarely adequate.

Subleukemic Leukemias. Thirty percent of leukemias present with a normal or subnormal white blood count. These cases are classified as subacute or subleukemic leukemia.

Confusion with aplastic anemia may arise if there is a history of exposure to toxic agents. However, a rapid onset is common in leukemia, while the onset of aplastic anemia is more insidious. As the leukemia develops hepatosplenomegaly and lymphadenopathy appear. There is a moderate to a marked degree of anisocytosis and poikilocytosis in the peripheral smear, and immature red and white cells may be present. More immature forms, predominantly blast cells, appear with the natural progression of the disease. The bone marrow usually shows leukemic proliferation with typical and atypical blast cells. On occasion the picture of leukemia may be difficult to differentiate from aplastic anemia especially when the bone marrow shows no blast cells. Time is the determining factor.

Megaloblastic, Macrocytic Anemias. A deficiency of vitamin B_{12} and folic acid result in a macrocytic peripheral blood smear. A bone marrow will reveal a megaloblastic change in most cases. Schilling tests, Folic acid excretion tests and gastric test meals confirm the diagnosis.

Hypersplenism

Primary hypersplenism implies simple splenomegaly and an associated hematologic abnormality with no obvious cause. Among the primary hypersplenic syndromes are included: primary congenital hemolytic anemia, primary idiopathic thrombocytopenic purpura, primary splenic neutropenia, and primary congenital panhematocytopenia.

Two interesting theories have been proposed to explain the pancytopenia that occurs: (1) stagnation of the blood in the spleen causes changes in the cells resulting in hemolysis, (2) a hormone from the spleen causes a direct suppression of marrow and of cell maturation.

Secondary hypersplenism denotes the depression of one or more of the formed elements of the blood, owing to some activity of the spleen which has enlarged as a consequence of a disease process. The organ may be affected in one of two ways. The venous outflow may be impaired and result in chronic congestive splenomegaly, which occurs in cirrhosis of the liver, Banti's syndrome, portal vein thrombosis, or splenic vein obstruction by thrombosis, splenic artery aneurysm, cysts, fibrosis or tumours of the pancreas. The spleen may be directly involved by the disease, which occurs in lymphomas, Boeck's sarcoidosis, Gaucher's disease, Felty's syndrome, miliary T.B., Hodgkin's disease, malaria, subacute bacterial endocarditis, infectious mononucleosis, and psittacosis.

Disseminated Diseases

Disseminated Lupus Erythematosus. Variable signs and symptoms are characteristic of the collagen disease, disseminated lupus erythematosus. Thrombocytopenia is common, resulting in petechiae, hemorrhages, and bleeding. A normochromic anemia with leucopenia is

present but may not be as extreme as the thrombocytopenia. Blood casts and albumin are found in the urine; a weakly positive Coomb's test, increased ESR, increased serum globulins, positive Wasserman reaction, decreased serum complement, and a positive LE cell test help make the diagnosis.

Disseminated Tuberculosis. Pancytopenia may be a presenting manifestation of disseminated tuberculosis. Fever, sweats, loss of weight, malaise and splenomegaly are common. Tubercles may be found in the bone marrow. Acid fast bacilli may appear in the smear or the marrow cultures may be positive for tuberculosis. Too much emphasis may be put on the skin test and chest x-rays which are frequently negative.

TREATMENT

Treatment of the pancytopenia will depend on the nature of the underlying cause if one is present. Malignant infiltration is best handled with roentgen therapy and/or chemotherapy. Disseminated lupus erythematosus is treated with corticosteriods, and disseminated tuberculosis with triple therapy. Other features of treatment are listed below.

Supportive

Anemia. Since a moderate amount of anemia stimulates the bone marrow, sufficient transfusions are given to keep the hemoglobin between 9 and 10.5 grams. Platelets are provided by fresh whole blood. Patients receiving transfusions for prolonged periods become increasingly susceptible to transfusion reactions, and may develop hemosiderosis and hemochromatosis.

Infections. Broad spectrum or specific antibiotics are used in active cases of infection but long term antibiotic therapy is not advocated. When recovery from infections is slow, the possibility of agammaglobulinemia must be considered, and if present will require the use of gammaglobulin.

Bleeding. Fresh whole blood supplies platelets to control the hemorrhage but carries with it the danger of the complications noted earlier. Corticosteriods may be given a trial, or splenectomy may be beneficial.

Stimulation of the Marrow

Corticosteriods. Steroid therapy stimulates the marrow and decreases antibody production. Prednisone, in doses of 50 to 100 mgms. daily, is used for a three week period and withdrawn if unsuccessful.

Splenectomy. Removing the spleen decreases the destruction of the red blood cells. Fewer transfusions are often required after a splenectomy. However, in cases where the spleen has assumed the function of the bone marrow, a splenectomy is harmful.

Hormones. The best response to therapy to date has been seen in children with the administration of hormones, but the results in adults have been disappointing. Testosterone in doses of 1 to 2 mgms./kgm. daily, plus triamcinolone, 8 to 20 mgms. daily is given. Maintenance therapy may need to be continued if successful.

Dimercaprol. (EDTA). Dimercaprol is used for bone marrow suppression secondary to the use of gold or arsenicals. It removes the metal from the tissues through its chelating action and allows it to be excreted in a harmless form.

Other Methods

Factors to stimulate the production of erythropoietin are not in practical use. The levels of erythropoietin are increased in aplastic anemia.

Marrow transplants have been tried, mainly experimentally, and have only been successful in cases of identical twins.

Prognosis

The prognosis will depend in a large number of cases, on the underlying cause of the pancytopenia. The prognosis is poorest for those suffering from caricinoma metastases, malignant lymphomas, multiple myeloma, and the leukemias. And the prognosis is best for those suffering from a treatable, and perhaps curable disease. There are no good correlations between the severity of the bone marrow depression and the prognosis of the disease.

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Medical Horizons

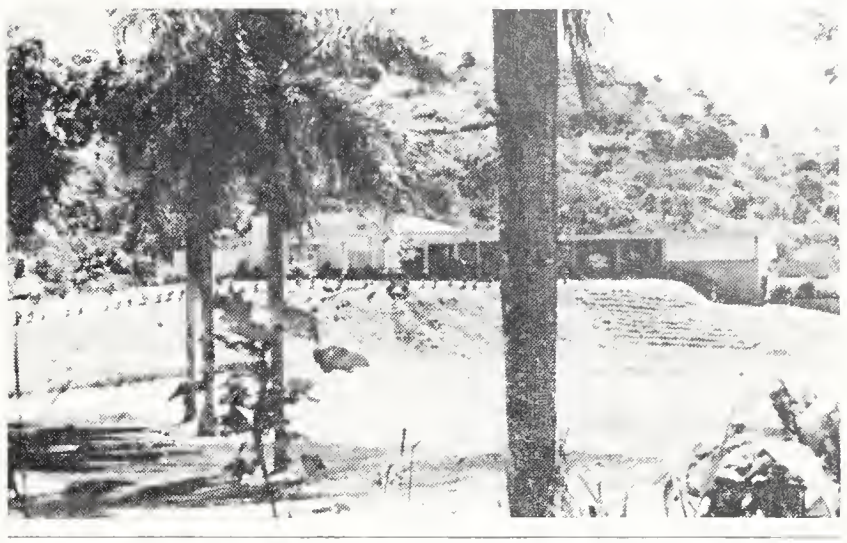
A SUMMER IN PUERTO RICO

When one is confronted with the final free summer of his "career" which has thus far been spent within institutions of learning, a decision must be made as to how it might be best spent. The thought of travelling abroad to strengthen the facets of education which have thus far been neglected is entertained. But, because of five or six years of training, there is also the desire to justify the time and money which have been spent thus far on preparation, and an effort should be made to gain some practical experience within the broad field of medicine.

It was the combination of 'justification' and 'wanderlust' which set me on the path to the small rural community of Castaner, situated in the mountains on the western part of the island of Puerto Rico. Here, in a basic atmosphere of Spanish culture which has become deeply permeated by the American way of life, I was exposed to a health service project of exceptionally fine calibre.

Nestled within hills blanketed with coffee shrubs, banana, citron, and citrus fruits lies the Hospital General de Castaner, administered by the Brethren Service Commission of the Church of the Brethren, Illinois. Throughout the past twenty years, this organization has developed health services in the Castaner valley region from a state of non-existence to one today which might be termed unique in the eyes of those who have been associated with it. At present, the centre of the health project is a beautiful but functional ranch-style, 33-bed hospital opened in 1960 with equipment and facilities which equal, or surpass those found elsewhere on the island.

One portion of the work centres around the hospital and its 33 beds divided into eight obstetrical and eight paediatric, with the remaining for surgical and medical cases. The character of many of the general case work-ups differs little from what might be found on the wards in any general hospital in Canada, but there are many interesting situations peculiar to the region. Not the least amongst these were symptommatic parasitic infestations accompanied by primary and/or secondary anemias and malnutrition. Chief offender in this situation was *Ascaris lumbricoides* with up to 90% of children, and 60% of adults showing ova in their excreta. Other intestinal nematodes often contributed to the clinical picture and *Enterobius, Trichuria, Ucinaria,* and *Trichostrongulus* were outstanding in this respect. The prevalence of these helminthic diseases in a tropical area such as Puerto Rico is



dependent mainly upon the presence of the appropriate hosts, higher temperature and humidity, poor personal and environmental hygiene and particular racial food habits. The first and second factors are relatively established, and irreversible, but the latter two are malleable, and it is to this end that much of the public health and social work of the project is aimed through a combination of medication, demonstration, and education.

Public health is a second portion of the work. An interesting experience in the public health work is the weekly trip to one of four "out clinics" held at varying distances from the hospital, and accessible in three of the four instances only by a vehicle equipped with four-wheel drive. We had an indispensible Land Rover for this purpose. Accompanied by a team of one R.N., two practical nurses, and the social worker, the doctor examines from 50 to 90 children and adults in the period of a working day, and basic immunizations are either initiated or continued, specimens of excreta are collected and returned to the hospital laboratory for examination, and medications for this, and other ailments are given when necessary. Occasionally, we brought a child back with us to the hospital for further therapy or investigation. These monthly clinics are, for some, their only contact with "medical" personnel (unless there is a *spiritista* in the area) and permanent records are kept by the hospital concerning their medical history.

A third, but by no means minor phase of the work at Castaner is centred around the Emergency-Out Patient Department of the hospital where, for 4½ days of the week, from 60-80 patients are seen daily in one of the pre- or post-partum, well-baby, TB, diabetic, and general clinics. These clinics, run on a private and public basis, constitute a time-consuming but much-needed service since there is only one private doctor in the entire region serving a population estimated to be around 18,000 people. A full dental programme is incorporated into the OPD as well, with the latest in

facilities, and a competent staff of one dentist and two assistants.

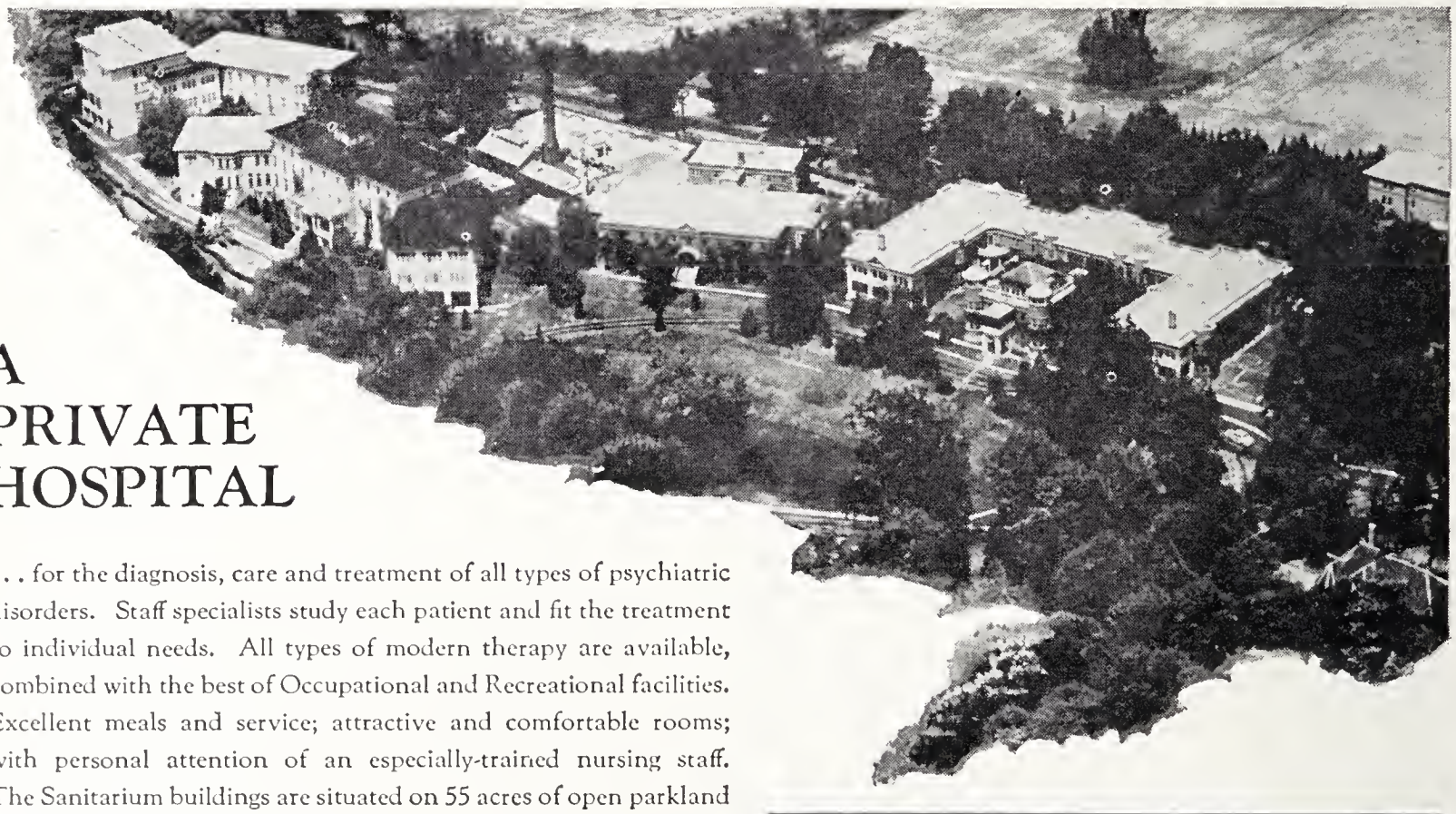
Here in Castaner, in such an isolated locale, one would not expect to find a programme of research in operation, but such is not the case. The hospital and the people of the area have contributed greatly to the assessment of the effectiveness of oral contraceptives during their early experimental investigation, and at present Dr. Adaline Pendleton, one of the pioneers in the field of Family Planning operates regular clinics at the hospital as part of her programme of testing a new intra-uterine birth control device. Here in the centre of the warm womb of the world, it seems imperative that some form of effective contraception must be encouraged if serious consequences are to be avoided.

The hospital maintains close relations with the Medical School of the University of Puerto Rico in San Juan and in particular with the Departments of Medical Zoology and Parasitology and is regarded as the main rural hospital to which students and inter-American Fellows are sent for demonstrations and study of the parasites found, and living conditions endured in the area. The programme also includes the testing of the effectiveness and evaluation of various new drugs in eradicating parasitic infections, case-finding, and the supplying of parasitic specimens for university teaching purposes.

Lest it be assumed that all hours were spent on the job, I must point out that I had many opportunities to travel to various spots of interest around the island including a trip to JKF's Peace Corps Camp at Dos Bocas, visits to San Juan and Ponce, the two largest cities on the island, hiking and mountain-climbing, swimming and fishing, attending the Pablo Casal's Music Festival and a three-day trip to the Virgin Islands, but to mention a few. An appreciable amount of time was spent learning Spanish, but as the summer drew to a close, I actually felt that the language barrier was diminishing, if only slightly, and I was better able to appreciate the people and their customs because of this.

Such was my summer of 1962, and after this investment of such a brief time, I feel that I have reaped gains one-hundred fold and more in friendships with both the *Americanos* and *Puertoriquenos,* as well as in experience, inspiration, and education, and would recommend a similar venture for anyone interested in benefits other than monetary for their final summer at Medical School.

John R. Taylor 6T3



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Upper Gastrointestinal Bleeding

S. R. McNeill 6T4

The author presents a comprehensive discussion of the clinical approach to Upper GI bleeding with comments on appropriate treatment.

From the point of view of early treatment as well as differential diagnosis, upper GI bleeding is a common and important medical condition. This article suggests one clinical approach in dealing with the problem. The *immediate* problem is to determine the extent of hemorrhage and to control it. The *early* problem includes a differential diagnosis of the hemorrhage and definitive treatment.

Evidence of Bleeding

Hematemesis is the vomiting of blood from the GI tract, usually dark in colour and resembling coffee grounds, but may be bright red and copious. It may be mixed with food particles.

Melena is the passage of black digested blood in stools. During the passage through the intestine, the blood undergoes chemical change. Massive hemorrhage may be a stimulus to diarrhea and melena will appear early; rarely frank bleeding per anum is noted, but this usually indicates lower GI bleeding.

It is necessary to be aware of three spurious sites of hemorrhage: bleeding from mouth after oral operation; from the nose after nasal operations; and coughing of blood from the lungs which may give rise to swallowing and vomiting of blood.

IMMEDIATE PROBLEM

Extent of bleeding

For purposes of coming to a quick and organized conclusion as to the severity of hemorrhage, the following classification is offered:

Grade I	occult bleeding — iron deficiency anemia with Benzidine positive stools.
Grade II	single hemorrhage without shock.
Grade III	single or repeated hemorrhage with shock.
Grade IV	massive exsanguinating hemorrhage.

For practical purposes and immediate attention, one must consider bleeding of Grade II and III severity. Grade I is so slight that time usually is not a critical factor; Grade IV is so massive, that death is the usual outcome.

History. On first examination, it may be difficult to determine the amount and severity of bleeding. Individuals will report wide variations in volume of blood lost. It is often helpful to ask the opinion of a friend or relative or eyewitness. A history of a large volume loss cannot be ignored. On the other hand, a history of absence of large blood loss does not rule out a severe hemorrhage.

Cardiovascular Status. Some clinical signs are useful in assessing the severity of a hemorrhage.

Blood Loss	*Skin Color*	*Pulse*	*Resp.*	*B.P.*	*Hbg.*
Mild — less than 500 c.c.	— —	— —	— —	— —	— —
Moderate — 500 to 1000 c.c.	Cyanosis	Incr. +	Incr. +	Decr. +	Decr. +
Severe — more than 1000 c.c.	Cyanosis, Pallor	Incr. ++	Incr. ++	Decr. ++	Decr. ++

A *mild* hemorrhage may present with few clinical signs. However, such a hemorrhage in an anxious individual may result in a rapid pulse, and increased respiratory rate, simulating a more severe blood loss. Sedation will often calm this type of individual and reveal the true status of the cardiovascular system. Depending on the degree of cardiovascular compensation, a mild hemorrhage will present the most variable signs. The pulse may be increased or normal, and the B.P. decreased, or normal.

The classical signs of shock, or impending shock such as a rapid thready pulse, falling B.P., cold, pale skin and restlessness are usually noted in a *severe* hemorrhage. The diastolic B.P. reflects the decrease in blood volume better than the systolic reading. A diastolic level of 60-65 mm Hg usually indicates a moderate to severe hemorrhage.

Age and Health of Patient. Hemorrhage in an older patient will have more severe consequences than in a younger one. There are usually more diseases superinposed on the GI lesion as age increases, and it may be more difficult to appraise the severity of any hemorrhage due to some degree of limited ability to compensate for blood loss in the aged.

Immediate Control of Hemorrhage

The immediate objectives in treating the patient are treating the shock, and stopping the bleeding. It may be difficult to distinguish between Grade II and Grade III hemorrhage, and the threat of a Grade II becoming more severe, or recurring will require that the same basic principles be applied in both cases.

A mild Grade II hemorrhage may be treated conservatively at home. Bed rest is indicated, and close observation advised.

More severe Grade II and Grade III losses require:

1. Immediate hospitalization
2. Both medical and surgical assessment from the time of admission
3. Warmth and bed rest with feet elevated to aid blood supply to the head
4. Morphine gr. ¼ S.C. to allay anxiety, and in 2 hrs. if needed
5. IV using #18 needle; Glucose and water, or other suitable expander; blood sample for type and cross match
6. Blood transfusion depending on the degree of shock and the cardiovascular status (More harm will result from transfusing too little blood than too much. Packed RBCs are excellent in older patients. Usually the initial bleeding will stop within 12-24 hrs. after addition of 1500-3000 cc of blood.)
7. Duodenal tube as a diagnostic aid in determining location and recurrence of hemorrhage
8. Sengstaken-Blakemore tube if clinical evidence points to cirrhosis and esophageal varices as the site of the bleeding (Cessation of bleeding after esophageal tamponade is almost diagnostic of varices.)
9. Observation of the patient closely for 12-36 hours, taking B.P. and pulse q½h (This is a critical time, because recurrent hemorrhage usually occurs within this interval.)

If bleeding continues despite the above measures, then two choices are open: continuation of medical treatment, or consideration of and preparation for surgery.

Medical. Blood transfusions are employed to restore any blood lost using whole blood in most cases. Supportive therapy including sedation and catheterization is continued. Gastric lavage using iced water or saline, 50 c.c. at a time is repeated through the duodenal or Blakemore tube. It may be neccssary to check the blood clotting factors.

Surgical. Preparation for surgery includes restoration of blood loss, maintenance of the cardiovascular state as close to normal as possible, and the elimination of any infection. The indications for surgery are discussed under difinitive treatment.

EARLY PROBLEM: DIAGNOSIS

The site of bleeding may be anywhere from the esophagus to the first part of the jejunum.

Site:	*Lesion: Common*	*Less Common*
1. Esophagus	Varices; ulceration	Ca; Ruptured Aortic Ancurysm
2. Stomach	Peptic ulcers; Ca; Gastritis	Hiatus Hernia; other neoplasms
3. Duodenum	Peptic ulcer	Diverticula; Gall stone erosion; post bulbar ulceration
4. Jejuneum	Stomal ulcer	

Miscellaneous rarer causes include:

1. *Traumatic*: Foreign body, burns, Mallory Weiss syndrome (the strain of vomiting causing small lacerations of the cardio-esophageal junction.)
2. *Blood Diseases*: Haemophilia, idiopathic thrombocytopenic purpura, thrombasthenia, Von Willebrand's disease
3. *Neoplasms*:Benign (leiomyoma, adenoma, lipoma, neurofibroma), Malignant (leiomyosarcoma, and lymphosarcoma, both rare).
4. *Vascular*: Local GI thrombosis, aneurysms, telangiectasia, and hemangiomatosis
5. *Drugs*: Salycilates, Phenylbutazone, corticosteroids, and anticoagulants
6. *General Disease*: Periarteritis nodosa, malignant hypertension, uremia, nyelomatosis, amyloidosis, psychiatric (self-inflicted), Krohn's disease, and others.

Approximately 98% of upper GI bleeding is due to one of five distinct conditions.

Chronic duodenal ulcer	40%
Chronic gastric ulcer	30%
Acute gastric erosion	20%
Cirrhosis of liver with varices	5%
Carcinoma of stomach	3%

If there is nothing significant in initial examination to point to one of the numerous but rare causes of bleeding, then one must weigh the evidence in terms of one of the abovementioned common conditions.

History

Often a complete and detailed history contributes the important information which leads one to a clinical diagnosis. It is necessary to consider the past health, family history, and personal history in detail, because the GI system, more than any other, reflects the insults and injuries of daily life. Gastrointestinal symptoms must be examined thoroughly. In some cases, hematemesis will be prominent; in others, melena; but more often, the main symptom will be one of pain, dysphagia, dyspepsia or anorexia or a combination of these.

A GI hemorrhage in patients under forty is probably due either to duodenal ulcer, or acute gastric erosion. In the over forty age group, duodenal ulcer is still common, but now it is important to consider three additional lesions: gastric ulcer, cirrhosis, and gastric carcinoma. In the elderly patient (over sixty) it is im-

portant to rule out gastric carcinoma as the cause of a GI bleed.

Lesion	*Under 40*	*Over 40*
Duodenal Uleer	Very Common	Common
Gastrie Ulcer	Infrequent	Common
Aeute Gastrie Erosion	Common	Common
Cirrhosis & Variees	Infrequent	Common
Gastrie Careinoma	Rare	Common

Gastrointestinal lesions and hemorrhages are more common in males.

A *family history* of hemophilia, purpura, or Vitamin K deficiency is significant in any patient with GI bleeding. A thorough investigation is indicated. Similarly, the patient may give a family history of peptic ulceration, and this too is significant in considering the cause of an upper GI hemorrhage.

Personal History. Details of personality, life experience and living habits may give some help in diagnosis. Some of the more important facts to establish are occupation, personality and habits concerning alcohol, eating, sleeping and the use of drugs. The clue to diagnosis of the specific cause is often found in one of the above factors. A patient with rheumatoid arthritis has been taking large doses of salycilates. If this person presents with upper GI bleeding one would think strongly of acute ulceration precipitated by the drug. On the other hand, a patient may present with a long history of alcoholism. This fact does not rule out any one cause of bleeding, but it makes one think strongly of cirrhosis with esophageal varices.

These details in history are never sufficient to give a diagnosis. However, they will help by pointing to one or another of the causes, and by supporting other evidence.

GI Symptoms

A detailed account of the mode of onset, duration, and progression of gastrointestinal symptoms is usually the most important part of the history obtained. In one series of cases, Gow and Mullens found that a history of proven peptic ulcer or significant dyspepsia was given by 154 out of 174 patients on admission for treatment for GI hemorrhage.

Lesions in the GI tract are expressed by a limited number of symptoms. Some of the more important features are *anorexia, pain, nausea, vomiting,* and *regurgitation*. Therefore, any group of GI lesions must share these symptoms in different sequences and combinations. It is important to try to identify a pattern of symptoms which is commonly seen in one disease, and which is sufficiently different to allow distinction to be made from another. Often however, the patterns are not constant, and are not defined to such an extent that distinction can be made from symptom patterns of other diseases. Although rarely diagnostic, GI symptoms are valuable in conjunction with other evidence.

Duodenal Ulcer. A long history of recurring and intermittant epigastric pain of 2-3 weeks duration followed by remission of symptoms for 2-6 months is strongly suggestive of chronic duodenal ulcer. Episodes commonly occur in the spring and fall. The epigastric pain comes on 2-3 hours after meals and is relieved by food and alkali. Hunger pains at night may be noted. Appetite is usually good, but many may avoid specific foods. Weight loss is usually not a significant finding. Occassionally a duodenal ulcer presents with hemorrhage and no pain.

Gastric Ulcer. A similar history of chronic and episodic GI symptoms is noted as for duodenal ulcer. Severe epigastric pain commonly occurs ½-2 hrs. after meals. Anorexia may be seen, and weight loss is a common observation.

Acute Gastric Erosion. A history of recent dyspepsia followed closely by hemorrhage is good evidence for acute erosion. There may be little pain or anorexia. Weight loss is not noted.

Gastric Carcinoma. Usually this begins as a diffuse, mild, and vague epigastric discomfort. It may become constant and painful and commonly the pain is aggravated by meals and unrelieved by alkali. Anorexia of long duration, and marked weight loss are very common and important symptoms.

Cirrhosis with varices. Usually very few GI symptoms are noted in this case. Anorexia and weight loss are common but usually in the later stages. In about 15% of cases of esophageal varices, there will be a coexisting peptic ulcer.

Nature of Bleeding

As a general rule, there is nothing particularly significant about the bleeding in any of the five important lesions to allow a distinction to be made on it alone. Each may present with only slight, or massive hemorrhage, and each may present with hematemesis and/or melena.

A gastric ulcer presents more often with hematemesis while a duodenal ulcer presents more often with melena. Gow and McGregor found that hematemesis was the presenting sign of bleeding from varices in 60 out of 80 cases. In bleeding from varices, massive hemorrhage is noted in approximately 50% of the cases and the mortality rate is in the order of 40%. However, in chronic ulceration, massive hemorrhage is seen less frequently.

It is important to know the number of previous hemorrhages. In a series of 174 cases of peptic ulceration, Gow and Mullen noted 43 had a history of more than one hemorrhage, most commonly occurring at intervals of 1-2 years. In a previous study, Gow and McGregor found that with a hemorrhage from esophageal varices the percent of patients dying was the same after each episode. After each hemorrhage, approximately ½ died within three days from shock and anemia. This trend was unaffected by the number of previous bleedings. They also found that if a patient survived the fourth week, the prognosis in that one episode was good.

Physical Examination

As far as arriving at a differential diagnosis, the physical examination may be disappointingly unrewarding. However, useful evidence is often found which supports other clinical findings. The physical examination is important in assessing the general health and physical state of the patient. This is significant in considering the effect of recurrent hemorrhage or the possibility of surgery.

Certain signs are commonly detected in specific conditions, but these signs are not constant, and as with symptoms relative to the GI tract, much individual variation is noted.

Duodenal Ulcer. Inspection may reveal little, except for a patient in distress, lying quietly. There may be some signs of muscle wasting. Deep tenderness in the epigastrium is usually noted, commonly on the right side.

Gastric Ulcer. The patient may appear pale and anemic with some associated muscle wasting and weight loss. Deep central tenderness in the epigastrium is commonly noted.

Cirrhosis. The general nutritional state of the patient may be quite poor with muscle wasting. Often associated are some of the common signs of liver cirrhosis: jaundice, spider nevi, palmar erythema, abdominal distention, and prominent abdominal veins. Hair loss in the female is significant as is gynecomastia in the male. Gross swelling of the legs may be noted. A vague, mild tenderness may be noted over the liver which may be enlarged. This may not be the case in the later stages of cirrhosis due to extensive fibrosis of the liver parenchyma. Splenomegaly is usually associated with portal obstruction. One can usually demonstrate ascitic fluid within the abdominal cavity and pitting oedema of the lower limbs is often seen.

Gastric Carcinoma. Pallor, accompanied by severe generalized muscle wasting is commonly seen with gastric malignant growth. Enlarged nodes should be sought for and special attention given to the sentinal node in the left supra-clavicular fossa. A vague mild deep epigastric tenderness may be noted, but this is usually less painful than that associated with chronic gastric ulcer. The left epigastrium should be palpated for a mass which is usually mobile and painless. Occasionally an enlarged, irregular nodular liver is detected due to secondary spread of the neoplasm. Rectal examination often reveals a rectal shelf due to secondary spread within the peritoneal cavity. Finally, ascites may be present due to pressure of metastases on portal venous flow and peritoneal seeding.

Investigations

There are two basic approaches to the investigation of GI hemorrhage. A vigorous early diagnostic approach utilizes X ray, secretory studies, esophagoscopy and gastroscopy. A staged, diagnostic approach investigating the actual cause and site are carried out at a later period, when the initial symptom and bleeding are treated fully by supportive therapy.

Radiology. A barium meal can be given in bed on the ward and X Rays taken with portable apparatus. The important feature is to avoid manipulation of the patient. By this method, 40% of esophageal varices will be revealed.

Secretory Studies. These usually show good supportive results in cases of ulceration. The principle here is to investigate the gastric free acid by intubation and aspiration of stomach contents. Five c.c. of fluid are drawn off hourly over a 24 hour period and the pH and presence of recent or old blood noted. Association of clear gastric specimens with evidence of continued blood loss indicates that the site of hemorrhage is in the duodenum. This method is also important in the detection of early recurrent hemorrhage since fresh blood may be seen in the hourly aspirations before changes in pulse rate and B.P. reflect the bleeding.

There are three important types of secretion abnormalities. High night acidity in which the pH of the sample is lower than 2.0 between midnight and 6 a.m. is characteristic of chronic duodenal ulcer. Nocturnal neutralization, in which a steep fall in acidity approximating falling alkaline levels is highly suggestive of chronic gastric ulcer. Achlorhydria is diagnosed when the pH of a majority of the sample aspirations during the night is more alkaline than 3.5. This is the typical finding in partial bleeding from acute ulcerative lesions.

Esophagoscopy and Gastroscopy. The use of the

gastroscope may reveal diffuse oozing of blood from an acute gastric erosion. It is important to detect these cases early because they usually do not require surgical intervention and do well on conservative management. Esophagoscopy and gastroscopy will help to differentiate varices, gastric ulcerations, and gastric carcinoma in most cases.

Avery Jones is of the opinion that the early diagnostic approach, utilizing the three abovementioned aids, represents a significant improvement over clinical impressions in determining the cause of bleeding. The vigorous early approach to diagnosis is particularly important if the bleeding is severe and definitive treatment must be started as soon as possible. If the hemorrhage is less severe, then a slow, staged approach to diagnosis is indicated.

DEFINITIVE TREATMENT

The key to treatment of GI bleeding is a combined *medical-surgical* approach. Numerous factors will influence the method of treatment, and some of the more important are age of the patient, amount of blood lost, recurrence of hemorrhage, location of the lesion and associated disease.

Medical Treatment

The general method of treatment is to continue efforts to stop the bleeding and treat the shocked state. If bleeding is effectively stopped by initial efforts, then conservative treatment is continued. This includes careful control of blood volume and electrolyte concentrations. Repeated BP and pulse readings every two hours, and determinations of serum Na, K, Cl, and CO_2 combining power.

A bland, soft diet with high caloric value and fluids *ad lib* are given. Sedations and antacids may help and the patient should be closely observed.

A fundamental principle in treatment is that both medical and surgical personnel are following the patient's progress. The important point is to know the indications for abandoning medical treatment and considering the possibility of surgical intervention.

Surgical Treatment

Indications. On an Emergency Basis *massive continuous* bleeding is an indication whether repeated early transfusions have controlled shock or not. A *history of bleeding* with stopping and recurrence is another indication. This usually refers to massive bleeding at short intervals.

Possible indications. A patient who is chronologically or physically in the *older age* group cannot stand many episodes of bleeding, therefore operation is more likely here than in the case of a younger person. The presence of severe *associated disease* together with the hemorrhage will be a more serious problem and possible an indication for surgery. In some cases there may be problems of *blood shortage* or a limited supply especially with a rarer blood type. Known *gastic ulcers* have less tendency to respond to conservative management than duodenal ulcers, and may be considered as only surgically amenable. Some patients may have experienced one or more *previous hemorrhages* and there may be controversy as to his current status and prognosis. If hemorrhage was preceeded by some other *severe complication* such as intractable pain, then there may be reasonably sound reason for surgery here. Surgical intervention may be the only means of controlling bleeding from esophageal varices if the tamponade effect of the *Blakemore tube fails.* Once the hemorrhage and shock are controlled and the acute phase is over, a patient may be considered as a surgical candidate if there have been several minor bleeding episodes previously, or some other indication.

Operative procedures. In any operative procedure, it is necessary to identify the site of hemorrhage and then to get control of the bleeding. The usual procedure for a benign bleeding gastric ulcer is partial gastrectomy. Two methods are employed with duodenal ulcers: ligation of vessels and combination pyloroplasty and vagotomy, and partial gastrectomy. Often radical gastrectomy is necessary to eliminate the neoplastic growth and affected nodes in gastric carcinoma.

Two methods are employed with esophageal varices. Shunting of portal flow to decrease the level of portal hypertension is often useful. A portocaval shunt is considered best, but often a splenorenal shunt suffices. A direct attack on the varices may be made. Transesophageal ligation of the varices may be carried out, or complete division followed by reformation of the esophageal-gastric junction.

ACKNOWLEDGEMENTS

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Recent Advances

TISSUE CULTURE AND CHROMOSOME ANALYSIS

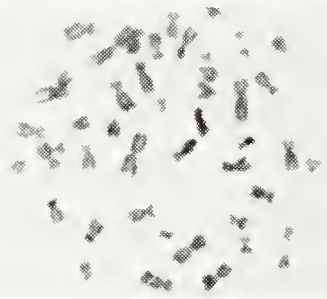
In *"Clinical Applications of Human Chromosome Studies"* (Recent Advances, U.T.M.J., Nov. 1962) the rationale for chromosome studies of human material was presented along with recent advances in karyotype interpretation. The present communication is intended to outline the technical advances in the cultivation of small biopsy specimens which have made chromosome studies possible. These techniques are the *sine qua non* of securing cellular material for cytological and/or biochemical investigations being adopted now by major hospitals throughout the country.

Chromosome studies of the mammalian cell require that the cell be engaged in active mitosis, for it is only in this stage that the chromosomes appear as discrete recognizable entities under the light microscope. This sole fact is the prime reason for using *in vitro* rather than *in situ* tissues for such investigations. The use of *in situ* tissues is limited to only a few types of tissue that show constant mitotic activity such as embryonic tissues, bone marrow and lymphoid organs. These are not at all practical for routine clinical procedures in which readily accessible tissues such as skin and blood are much more convenient. In tissue culture, besides securing a higher rate of mitosis, monolayers of cells can be plated so that treatment with hypotonic solution (to swell the cells and chromosomes) can be most effective and fixation is at its best. Proof of the superiority of the tissue culture technique is the fact that the accurate human karytope could only be constructed after in vitro techniques were employed.

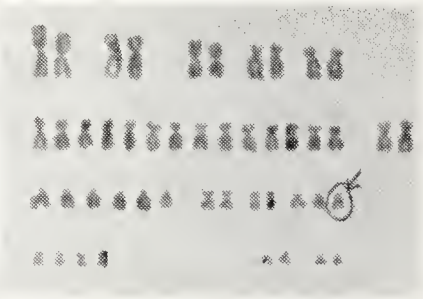
There are now many excellent methods for growing biopsy or autopsy specimens in tissue culture. The classical method, the use of a plasma clot to provide both nutrient and lodging substance for the tissue fragments, has several disadvantages in photography and subculture and as a result has been largely replaced by newer methods of using tissue fragments floating in a liquid culture medium in a culture vessel.

To get a high number of mitotic figures a culture must be in its maximum growth period. The "harvesting time" is ascertained by periodic microscopic examination of the culture. At this time colchicine (or a derivative e.g. colcemid) is added to the medium in small amounts and incubated for approximately one hour. This serves to arrest mitosis in the metaphase when chromosomes are large, intact, and composed of two chromatids joined at the centromere which have a characteristic size and shape, permitting grouping or karyotyping. Trypsin is then added to dissociate adherent cells and the separated cells are exposed to hypotonic solution for five to ten minutes. The cells are fixed in acetic acid and stained in acetic-orcein solution.

The final step is making a "squash" preparation by putting a small drop of the above cell suspension on a glass slide, covering it with a cover slip and pressing down on this with the thumb thereby flatenning the cell and spreading out its chromosomal contents. The chromosomes can now be examined under a light microscope (dark field, phase, etc.,) and can be photographed. From this photo chromosomes can be cut out and arranged in groups according to convention — the process of karyotyping. (see below)



Squash preparation of peripheral white blood cell.



Karyotype of "E" syndrome showing trisomy of chromosome #18.

The major criticism of using in vitro cells for chromosome studies is the possibility of heteroploid transformation (i.e. the number of chromosomes becomes other than normal diploid number of 46 during successive divisions), which would give misleading results. A serious difficulty has also been encountered in attempting chromosome analysis of tumours because of contamination of the culture with stromal elements. This can be partly overcome in epithelial cell tumours by distinguishing cell types on the basis of morphology. However in tumours of connective tissue origin this is a veritable impossibility.

In spite of these obstacles, a steady stream of advances are being made in the field of tissue culture and chromosome analysis. The clinical knowledge to be gleaned from these promises to be vast.

H. Tanzer 6T4

Biliary Cirrhosis — Human and Experimental

R. Baumal 6T3
M. Cooper 6T4

Clinical features and principles of treatment here accompany the etiology, pathology and experimental lesions for the three types of this rather rare but interesting condition.

HUMAN BILIARY CIRRHOSIS

Biliary cirrhosis is dominated clinically throughout most of its course by biliary obstruction with jaundice, and progresses to a fatal termination after a certain degree of hepatic cell insufficiency has been reached. Pathologically, it is characterized by alterations of cirrhosis in general — liver cell destruction, nodular hyperplasia, diffuse fibrosis, and in addition it possesses distinct features of its own.

Classification

Some workers have used a single term to include all stages in the development of biliary cirrhosis, whereas others have employed two or three terms to designate different phases of a single, continuing process. In the terminal stages of the disease, the anatomic and functional alterations become identical with those of portal or posthepatitic cirrhosis. Thus the classification has presented considerable difficulties[14].

The numerous proposed classifications have been summarized by Cameron and Hou in their recently published monograph "Biliary Cirrhosis"[1]. Their compromise classification is the one to be employed in this account:

1. Cirrhosis from obstruction of extrahepatic bile passages.
2. Primary biliary cirrhosis with inflammation of the intrahepatic bile ducts. This is also known as Hanot's hypertrophic cirrhosis, and by at least fifteen additional different names.
3. Canalicular stasis. This may constitute only a stage in the evolution of the disease.

Etiologic Factors

Cirrhosis from obstruction of the extrahepatic bile passages. The term biliary cirrhosis was originally used to designate the particular pattern of the liver lesions following prolonged obstruction of the common bile duct[14]. This may be due to carcinoma of the head of the pancreas, stones in the common or hepatic bile ducts, tumours of the bile ducts and ampulla of Vater and post-operative strictures of the ducts. In children, congenital atresia of the extrahepatic bile ducts is a rare, and often fatal, cause of biliary cirrhosis. Prolonged obstruction leads sooner or later to infection, which complicates the clinical and pathologic pictures.

Primary biliary cirrhosis with inflammation of the intrahepatic bile ducts. The cause of this condition is unknown. An autodestructive process has been suggested as an explanation. In one study, a 38 year old woman exhibiting the classic manifestation of primary biliary cirrhosis was found to have highly elevated titers of circulating complement-fixing antibodies to liver, kidney and other human tissue antigens[10]. This finding has been confirmed in additional patients[11]. Other workers have shown that the serum gamma globulin of patients with liver disease becomes bound to the cytoplasm of biliary epithelium[17]. These findings suggest that some cases of primary biliary cirrhosis may result from an antigen-antibody reaction occurring in the terminal intrahepatic biliary passages, and rendering them more permeable, so that bile can re-enter the blood stream from the bile ducts. A comparable type of injury is seen in the kidney where in glomerulonephritis, injury due to an antigen-antibody mechanism renders the capillary endothelium more permeable to serum proteins. There is, however, no proof that circulating autoantibodies are in fact autodestructive and the possibility cannot be denied that they are an epiphenomenon, i.e. that they appear as a consequence of the disease rather than causing it.

Some investigators favour an infective etiology, yet no definite causative bacterial agent has been discovered[16]. Viral hepatitis and homologous serum jaundice, however, may pass through a phase in which intrahepatic obstruction dominates the picture. On occasion these diseases might run a prolonged course that culminates in post-hepatitic or portal cirrhosis. There is a growing feeling, and some evidence from serial biopsy studies, that acute or insidious cholangiolitic viral hepatitis may precede some cases of primary biliary cirrhosis[4].

Canalicular statis. This condition is seen following the administration of chlorpromazine, anabolic steroids such as methyltestosterone and norethandrolone. In the past, it had been attributed, largely on clinical grounds, to hypersensitivity[5]. Such findings as a past history of allergy, a latent period of 5-9 days before onset, the presence of urticaria, arthralgia, fever and eosinophilia, and beneficial therapeutic results from cortisone were considered significant. However, direct immunologic methods have not supported this concept. This has led to an alternative suggestion — that the etiology may be an enzymatic defect in liver cells[1].

Clinical features

The clinical course of all types of biliary cirrhosis can be considered as three distinct stages, which however, overlap considerably[12].

Stage 1. This, the longest phase, is one of *obstructive jaundice*. In the case of an impacted stone, jaundice usually has a sudden onset, progresses rapidly, and is accompanied by upper abdominal colic. The jaundice of neoplastic obstruction is frequently insidious and may be remittent if the obstruction is partial. Jaundice, present at birth, or appearing shortly thereafter and persisting, should raise the suspicion of congenital biliary atresia. In the early stages of primary biliary cirrhosis, the outstanding feature is chronic, insidiously developing jaundice. With canalicular stasis, jaundice appears suddenly or insidiously 2-3 weeks after ingestion of an incriminating drug, and lasts on an average, about 40 days. The course is almost always reversible, with 100% recovery after removal of the drug, although rarely, the picture may progress to full blown biliary cirrhosis.

Clinical features in this stage, in addition to jaundice, include: fever and weakness; anorexia and malaise; pruritis, which is especially severe and may be the chief complaint in primary biliary cirrhosis, and the passage of pale stools and dark urine. The appearance of a palpable spleen and hard, non-tender liver, marks the onset of stage 2.

Stage 2. The gradual onset of symptoms and signs suggesting *portal hypertension* — hepatosplenomegaly, oesophageal varices with hematemesis and bleeding per rectum, a prominent abdominal wall collateral circulation, ascites — is typical of this stage. Obstructive jaundice of stage 1 persists.

Due to the failure of bile salts to reach the intestine and emulsify dietary fat, intestinal fat absorption falls and steatorrhea ensues. Accompanying defective mineral and protein absorption leads to osteomalacia and osteoporosis, while decreased absorption of fat-soluble vitamins A, D and K may lead to clinical manifestations of these deficiencies.

The appearance of marked wasting foreshadows the onset of stage 3.

Stage 3. This stage of *liver failure* is characterized by signs and symptoms of the two previous stages in addition to those of hepatocellular insufficiency. Jaundice worsens. Hematemesis may be recurrent and prove fatal; the stools are often black. Ascites and intractable edema progress, and the patient gradually lapses into coma and dies from hepatic insufficiency or intercurrent infection. This phase is shorter than the others, and may last only a few months.

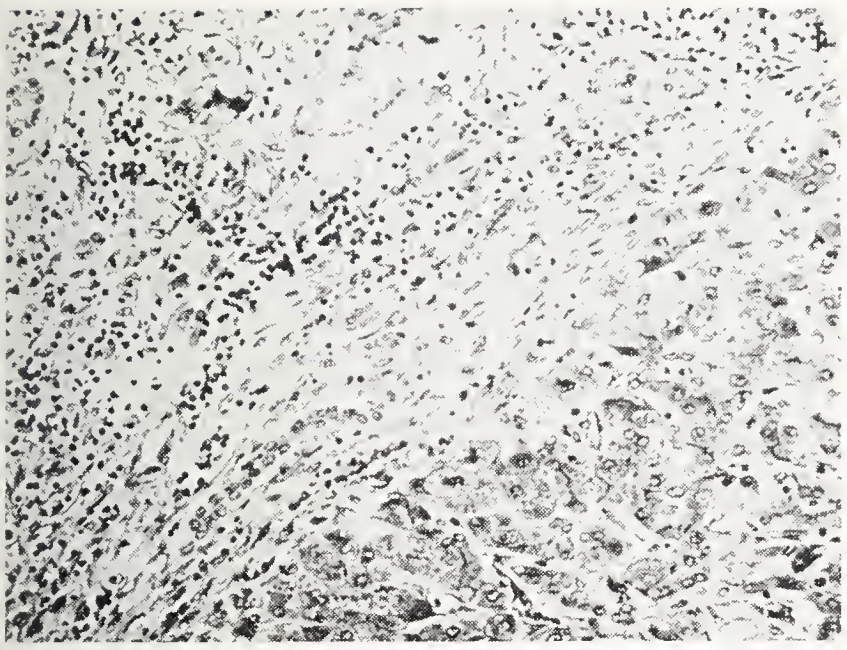
Biochemical features

There is little to distinguish between the variants of biliary cirrhosis insofar as chemical findings are concerned, such differences as exist being in degree, and not in kind[13].

During the whole of clinical stage 1, and for the greater part of clinical stage 2, the laboratory findings suggest only an *obstructive jaundice*. The stools are pale and contain excess fat, the urine is dark and contains bile salts and pigments. The serum bilirubin is persistently elevated, both indirect and direct-reacting (positive direct van den Bergh reaction) while the serum alkaline phosphatase level remains very high throughout. The bromsulfalein test is usually positive, indicating retention of dye because of blocked bile ducts.

As the disease progresses towards clinical stage 3, biochemical features of *hepato-cellular insufficiency,* in addition to those of obstructive jaundice, may be found. The serum bilirubin level rises still higher. Hypoproteinemia develops, the albumin-globulin ratio falls, and may become reversed. Flocculation, galactose tolerance and hippuric acid synthesis tests point to reduced liver function.

Total serum cholesterol and serum lipoproteins are elevated throughout all stages, and in some cases of primary biliary cirrhosis, may reach exceedingly high values[20]. When the serum lipids reach values of 1800 mgm% and higher and persist for at least four months, xanthomatous skin deposits consisting of flat xanthelasma about the eyes, nodular xanthomas on extensor surfaces, and yellow lines in the palmar creases, may appear. This form of the disease may be accompanied by a proliferation of lipid-laden histiocytes in portal areas of the liver and in other organs, and was known in the past as xanthomatous biliary cirrhosis. It is now recognized as yet another variant of primary biliary cirrhosis[13].



Masson's trichrome stain × *270.*

Fig. 1. Section of liver from a case of primary biliary cirrhosis. Periphery of a lobule can be seen in the left upper corner. The remainder of the section shows a widely expanded portal tract in which bile ductules can be recognized either as rosettes or trabeculae. There is a moderate pericholangiolitis present.

During the most advanced stages of the disease, as liver cell failure sets in, the production of lipids and bile salts is usually decreased, the pruritis is relieved and xanthomas, if present, disappear.

Pathologic Features

Cirrhosis from obstruction of the extrahepatic bile ducts. During clinical stages 1 and 2, the liver is enlarged, green in colour, hard, and finely granular. On microscopic examination, the earliest changes are canalicular and bile duct stasis, with bile thrombi distending these structures. Parenchymal liver cells and Küpffer cells are bile stained. Portal tracts are infiltrated with lymphocytes and polymorphonuclear leukocytes, indicating a peri-cholangiolitis. Granulation tissue proliferates and enlarges portal tracts and later penetrates between liver cell trabeculae. There is evidence of bile stasis in the form of "bile lakes" in the periphery of lobules. Regenerating nodules of liver tissue are not seen.

With progression of the disease, distention, proliferation and elongation of small bile ducts accompanies an ever increasing fibrosis of the portal tracts. The bile ducts and fibrous tissue spread around and into lobules dividing them into sectors, (pseudolobules), and the blood supply is disturbed and shunted past islands of degenerating and regenerating liver cells. At this stage, the lobular architecture is completely disorganized, and the clinical features of stage 3 appear. The liver is now shrunken in size and coarsely nodular. On morphologic grounds, the end stage of biliary cirrhosis bears a close resemblance to portal and posthepatitic cirrhosis, except for the presence of biliary pigment in the parenchyma, and the more abundant formation of new bile ducts.

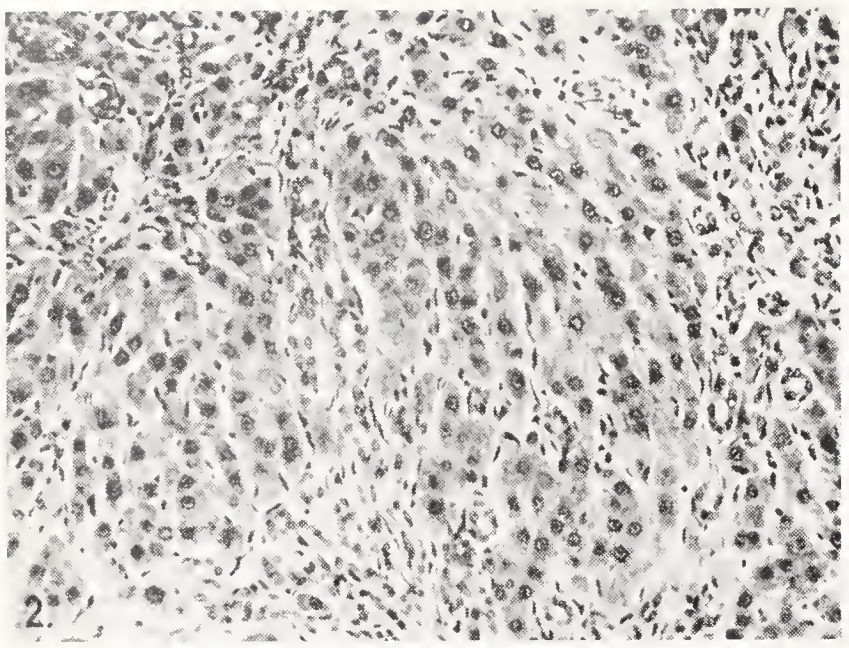
Primary biliary cirrhosis with inflammation of the intrahepatic bile ducts. The liver is enlarged, bile-stained, firm and finely nodular. The microscopic picture reveals that the most prominent change affects the smallest interlobular and perilobular bile ductules and the canals of Hering which form the connecting link between ductules and bile canaliculi. These are destroyed by a selective cellular injury which is accompanied by an acute inflammatory response. As a result, there ensues a loss of continuity of the biliary conducting channels at a site between the bile canaliculi and larger bile ducts. Not only is bile flow obstructed, with resultant pigmentation of liver and Küpffer cells and distention of canaliculi with bile thrombi, but bile continues to seep through the portal connective tissue. A granulomatous reaction develops in the portal tracts, thick bands of connective tissue form around some of the lobules and they penetrate focal periportal areas of destroyed liver cells, a process referred to as piecemeal necrosis. Proliferation of bile ducts occurs only after many months of obstructive jaundice, but the continuity of the cholangioles is not re-established, and this may prolong and make permanent the obstruction.

In long-standing progressive cases, the fibrosis becomes so severe, that a picture is produced which is virtually identical with that of the cirrhosis induced by obstruction of the extrahepatic bile passages.

Canalicular stasis. The liver is smooth, may be bile-stained, but is not enlarged. The most prominent microscopic feature is the presence of bile thrombi in canaliculi in centrolobular areas in which bile stained parenchymal liver and Küpffer cells abound. An inflammatory cell infiltrate may be present in portal tracts but the bile ducts are unaltered. Liver cell degeneration is seldom prominent. Inflammation of the canals of Hering is sometimes present and thus canalicular stasis may occasionally progress to full-blown biliary cirrhosis.

Principles of Treatment[18,20]

Primary biliary cirrhosis with inflammation of the intrahepatic bile ducts. Since the cause is unknown, the only treatment is symptomatic. Steatorrhea is treated with a high protein, low fat diet, with supplemental calcium and water-soluble preparations of vitamins A, D, and K. Relief of pruritis may be obtained with sublingual methyltestosterone, 25 mgm. daily, although this may cause an increase in jaundice. When portal hypertension and liver cell failure supervene, the use of diuretics, paracentesis and porto-caval shunt must



H. & E. × 270.

Fig. 2. Experimental biliary cirrhosis in a rat fed A.N.I. (0.1%) for a period of 33 days. Note large numbers of newly proliferated bile ductules which are surrounding and infiltrating a lobule of liver cells. The lobule contains no central vein, which has been probably incorporated into the connective tissue and ductular cell trabeculae when the lobule was being dissected into sectors.

be considered as the specific indications arise.

While the biochemical features of primary biliary cirrhosis are ameliorated by the use of ACTH and cortisone, there is no evidence that the fundamental pathologic process is affected in the same way.

EXPERIMENTAL BILIARY CIRRHOSIS

Cirrhosis from Extrahepatic Obstruction

Rats, guinea pigs, rabbits and mice have been subjected to surgical ligation of the common bile duct[2]. The ensuing liver lesions simulate morphologically those of obstructive biliary cirrhosis of man. When the rat's common bile duct is ligated with a single ligature, biliary obstruction lasts for 3 or 4 weeks, during which time the intraductal pressure rises continuously to high levels, and is then relieved by spontaneous restoration of continuity of the duct. As a result, the severe bile stasis, bile duct proliferation and fibrosis in the liver disappear, and the organ returns to normal in a few weeks. Hence, intraductal pressure is an important factor in the etiology of biliary cirrhosis.

Other workers have shown that the volume of bile secreted per unit time, in conjunction with a rising intraductal pressure, causes bile to leak from distended ducts into the parenchyma. This acts as a perpetuating factor, and leads to the formation of necrotic areas located near portal tracts. They are ultimately replaced by fibrous tissue which contributes to the cirrhotic process. That bile is capable of initiating necrosis in the liver has been recently demonstrated by Holsti[8], who fed dessicated whole bile to rabbits and produced liver alterations resembling biliary cirrhosis.

Cantarow and Stewart[3] have shown that the intravenous administration to cats with obstruction of their bile ducts of sodium dehydrocholate, a physiologically active bile salt preparation, leads to marked regeneration of hepatic cells and retarded proliferation of small bile ducts. Since during obstruction bile acid formation is suppressed, these investigators suggested that a diminution of parenchymal cell regeneration and an increased regenerative activity of ductular cells may result. Thus as alternative explanation has been provided to explain the behaviour of these two cell types in biliary cirrhosis.

Moore[15] has shown in parabiosis experiments (joining two animals together so that they develop a common circulation), that when the common bile duct of one of the partners is ligated, the other develops severe biliary cirrhosis. A chemical factor, probably a component of bile, would seem to be concerned. These data point to the operation of a number of factors in the ultimate production of biliary cirrhosis due to obstruction of extrahepatic bile ducts.

Primary Biliary Cirrhosis

When rats are fed a chemical called alpha-naphthyl-iso-thiocyanate (A.N.I.), liver alterations appear which are virtually identical to those of primary biliary cirrhosis in man[9]. If given in large doses, an acute necrotizing cholangiolitis appears, followed by the destruction of the lining cells of the ducts of Hering. The necrotic ductal epithelium and debri plugs the ducts, leading to complete cessation of bile flow and jaundice.

Prolonged intoxication with A.N.I. leads to diffuse hyperplasia of the intralobular bile ducts. Epithelial buds grow out into adjacent liver lobules accompanied by newly formed connective tissue and blood vessels, and eventually completely surround the liver lobules to form pseudolobules. Throughout this process, there is no interference with bile flow. After the drug is discontinued, the liver's structure is eventually restored to normal. This experimental model leading to the production of the pathologic alterations of primary biliary cirrhosis by a chemical agent distracts from the operation of an antigen-antibody reaction.

Canalicular Stasis

When rats are fed norethandrolone the excretion of conjugated bilirubin into the bile is markedly reduced. Hepatic glucuronyl transferase activity is unaffected, suggesting that this agent interferes with the transport

of bilirubin from liver cells into bile. Electron microscopic studies show alterations of the bile canaliculi, consisting of dilatation, fragmentation and reduced numbers of microvilli. Cytochemical studies reveal decreased ATPase activity at these surfaces. Thus it appears that the bile canaliculus is the prime site of hepato-cellular dysfunction in drug-induced cholestasis and may be a manifestation of a basic disturbance in the excretory mechanism of liver cells[6].

SUMMARY

Biliary cirrhosis is a rare but interesting condition which at present is not completely understood. A few features of the human disease have been presented in a simplified and somewhat dogmatic account, but the situation is much more complicated and frought with controversy and numerous interpretations. In addition, a few features of the experimental disease have been pointed out with a view to elucidating the etiology and pathogenesis of the human condition. However the surface has not even been scratched.

ACKNOWLEDGEMENTS

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Questions — page 58

FIGURE 1: Essential Familial Hypercholesterolemia with Cutaneous Xanthomata.

This condition is inherited as an autosomal dominant and is characterized biochemically by hypercholesterolemia, hyperphospholipidemia and sometimes hyperglyceridemia and hyperuricemia. The cause is unknown but there is probably an abnormality in the homeostatic mechanism regulating plasma cholesterol concentration.

The disease manifests itself with xanthomatous involvement of the skin, endocardium, heart valves, coronary arteries and other organs causing death from myocardial infarction even in childhood. However, the disease may remain entirely occult, with only a slight elevation of plasma cholesterol. (The cholesterol esters and the free cholesterol increase proportionately).

The treatment is similar to that for atherosclerosis: maintenance of ideal weight, reduction of saturated fat intake and ingestion of safflower oil.

FIGURE 2: Milroy's Disease (Heredofamilial Congenital Lymphedena)

This condition, present from birth, is thought to be a familial disorder. Pathologically, it is caused by a faulty development of lymphatic channels, possibly with poor structural strength, permitting abnormal dilation and incompetence of lymphatic valves. This results in stasis of lymph with accumulation of increased amounts of interstitial fluid and lymphedema. Classically, the legs are the major site of involvement.

Clinically, in its early stages, the edema is pitting in character. Later replacement fibrosis occurs in the edematous regions, causing permanent enlargement and deformity; the skin areas become very susceptible to trauma, infection and ulceration. Treatment is by postural drainage, effective bandaging and surgical excision.

Lymphedema praecox a condition of unknown etiology, presents a picture similar to that of Milroy's disease but is usually less severe. This condition affects chiefly females between the ages of 10 and 25, usually beginning in the feet and progressing up the limbs.

Elephantiasis, caused by Wuchereria bancrofti or W. malayi, is essentially lymphedema, and often affects the lower limbs. The larvae migrate through the lymphatics to the lymph nodes, where they cause irritation, leading to inflammation and obstruction of lymph vessels. Repetition of this process for many years is required before complete obstruction of lymphatics and elephantiasis occur.

Other causes of acquired lymphedema are obstruction of lymph vessels by neoplasm, scar, operative removal of lymph nodes and fibrosis caused by x-ray thereapy.

FIGURE 3: Malignant Lymphoma (Lymphosarcoma)

Primary tumours of lymph nodes are known as lymphomas. The clinical manifestations of each of the lymphomas are extremely varied making differentiation on such grounds practically impossible. Areas commonly involved by the lymphomas are the lymph nodes, tonsils, spleen, thyroid, respiratory tract, digestive system, circulatory system, genito-urinary system, osseous system, skin, nervous system and special senses.

Classification and differentiation of the lymphomas is made on cytological grounds. Two general groups can be distinguished:

A. Simple histological pattern
   1. Reticulum cell sarcoma.
   2. Lymphosarcoma
      (a) Lymphoblastic Lymphoma
      (b) Lymphocytic Lymphoma.

B. Complex Histological pattern
   1. Hodgkin's Disease
   2. Follicular Lymphoma
   3. Clasmatocytic Lymphoma.

From the standpoint of lymph node morphology, there is no sharp distinction between lymphocytic and lymphoblastic leukemias and some of the conditions just mentioned; however, differentiation between leukemias and lymphomas can usually be made clinically.

Lymph node involvement is the most common symptom and is usually the presenting complaint in people suffering from lymphomas; the glands of the neck at first one side and then the other are usually the first affected in Hodgkin's Disease and lymphosarcoma. Usually the enlargements are painless. In the sarcoma group the glands are rubbery and discrete at first becoming matted later; in Hodgkin's disease, the nodes are firm; in carcinoma, the glands are stony hard. Cervical glandular enlargement may also be the first evidence of leukemia.

Other causes of lymph node enlargement are con-

genital abnormalities (lymphangiomas), infectious allergic reactions and metastases from malignant disease.

FIGURE 4: Secondary Carcinoma of Cervical Lymph Node.

The differential diagnosis is that of a lump in the neck. However, because of the lump's position, fixity, texture and appearance it is most likely to be a metastatic enlargement of a lymph node.

Cancer and tuberculosis are the commonest causes of asymmetric enlargement of cervical lymph nodes and of the two, cancer is far commoner. Furthermore metastases to cervical lymph nodes are much commoner than primary malignant tumours of cervical lymph nodes, which not infrequently begin as an enlargement of a single node. The other common cause of cervical lymph node enlargement, inflammatory hyperplasia can be discarded because of the absence of pain and tenderness.

Cervical metastases arise from tumours in tissues and organs situated below the clavicle as well as from primary tumours in the head and neck. Tumours of the stomach, rectum, prostate, uterus, bronchus, esophagus, breast and testis may present with a cervical node metastasis. Malignancies of the lip, oral mucosa, tonsil, larynx, tongue, pharynx and thyroid frequently spread to cervical nodes as well.

FIGURE 5: A bleeding tendency must be due to a vascular abnormality, a defect in the platelets (either quantitative or qualitative), or a defect in the coagulation mechanism of the blood.

Vascular abnormalities (i.e. nonthrombocytopenic purpuras) result in spontaneous hemorrhages into the skin and mucous membranes, resulting in the formation of petechiae, ecchymoses, and purpura. There is often a family history of a similar bleeding tendency. Examples of nonthromboyctopenic purpuras are the allergic purpuras (e.g. Henoch Schonlein), the symptomatic purpuras due to infections, chemicals, avitaminoses, chronic diseases, and those associated with increased capillary fragility.

The purpuras due to *abnormal platelets* (i.e. the thrombocytopenic purpuras) also present with hemorrhages into the skin and mucous membranes and cannot be differentiated from the nonthrombocytopenic purpuras on clinical grounds alone. Examples of thrombocytopenic purpuras are idiopathic thrombocytopenic purpura (ITP), the symptomatic thrombocytopenic purpuras due to chemicals (e.g. nitrogen mustards, phenobarbitol), certain foods (orris root), and snake venoms, thrombocytopenic purpuras due to infections such as infectious mononucleosis and subacute bacterial endocarditis, and those due to hematopoietic disorders such as leukemia and some anemias.

Hemorrhages due to *coagulation defects* can often be recognized clinically by their characteristic occurrence into joints, muscles and subcutaneous tissues as large hematomas following trauma. The classical examples are hemophilia, and bleeding due to excessive use of anticoagulants.

Laboratory tests are often necessary to distinguish the three general varieties of bleeding tendency. A white blood cell count, red blood cell count, platelet count, peripheral smear and differential count, and hemoglobin should be done. In the patient pictured the white blood cell count was 60,000; the platelet count was low; the peripheral smear revealed many early immature white blood cells (myeloblasts and neutrophilic myelocytes) and a diagnosis of myelocytic leukemia was made. However, often further laboratory tests are required in order to determine the cause of a bleeding disorder.

Vascular abnormalities are diagnosed by a normal platelet count, a prolonged bleeding time, and a positive tourniquet test.

The thrombocytopenic purpuras have, as a rule, a normal bleeding time and a normal tourniquet test, and of course a low platelet count with a prolonged clot retraction time because of the decreased platelet clot-retracting ability.

The hemorrhagic tendencies due to coagulation abnormalities also have a normal bleeding time, a normal tourniquet test and a normal platelet count, but a prolonged clotting time, which is normal in the other two bleeding disorders. Coagulation mechanism can be divided into three stages and tests are available which determine in which stage the coagulation defect is present. The thromboplastin generation test and prothrombin consumption test (serum prothrombin time) reveal an abnormality in stage one such as occurs in hemophilia; the fibrinogen level determination of the blood will reveal an abnormality in stage three such as occurs in hypofibrinoginemia; the prothrombin time measures the efficiency of stages two and three and is characteristically prolonged in a patient receiving Dicoumarol as an anticoagulant. It is important to remember that in some coagulation disorders the clotting time may be normal and diagnosis can be made only by doing the additional tests mentioned above.

FIGURE 6: Porphyria.

Porphyria is a term which embraces a group of diseases, each with unusual and characteristic clinical

manifestations which have in common the excessive excretion of uroporphyrin and coproporphyrin and or porphyrin precursors (alpha-aminolevulinic acid and porphobilinogen) in the urine and/or faeces. The porphyrin metabolic pathway is important for the production of protoporphyrin, one of the main components of hemoglobin.

Porphyria may be classified according to whether the excess quantities of porphyrins are synthesized in the bone marrow (Porphyria erythropoietica) or in the liver (Porphyria hepatica). Porphyria hepatica is further subdivided into:

1. Acute intermittent porphyria.
2. Porphyria cutanea tarda hereditaria.
3. Porphyria cutanea tarda symptomatica.
4. Unclassified.

The acute intermittent porphyria, transmitted as a mendelian dominant, is characterized clinically by periodic attacks of intense abdominal colic usually accompanied by nausea and vomiting, obstinate constipation, neurotic or even psychotic behaviour, and neuro-muscular imbalance. The cutaneous lesions, blistering on skin surfaces exposed to light, and erythema, are more characteristic of Erythropoietica porphyria and cutanea tarda hereditaria.

Chloral hydrate for sedation, opiates for pain and steriods are useful in treatment. Barbiturates precipitate acute attacks and should be avoided completely at all times.

S. M. Zweig 6T3

Abstracts —

Chronic Postrheumatic Fever (Jacoud's) Arthritis; New England Journal of Medicine, Vol. 267, No. 1, 5 July 1962.

Can rheumatic fever produce a chronic joint deformity? Two cases are discussed in this article and references are made to similar cases in past literature. These cases are characterized by (1) a history of severe rheumatic fever with repetitive attacks, or prolonged attacks (2) delayed recovery and associated stiffness in the metacarpal-phalangeal joints (3) a deformity consisting of flexion at the metacarpalphalangeal joints with some soft tissue swelling, ulnar deviation mostly in the 4th and 5th fingers, and perhaps some hyperextension in the proximal interphalangeal joints (4) the characteristic deformity being due to periarticular, fascial, and tendon fibrosis rather than sinovitis (5) tendon crepitus (6) inactive joint disease with few or no symptoms, little evidence of active sinovitis and good functional capacity (7) normal sedimentation rate. These conditions are associated with severe heart disease progressing eventually to heart failure and a negative test for rheumatoid factor.

The differential diagnosis includes (1) Ankalosing spondylosis associated with aortic valvular disease (2) Coincidental rheumatic fever and rheumatoid arthritis (3) Rheumatoid heart disease.

Abdominal Aortic Aneurysm with Bleeding into the GI Tract. Proc. of the Mayo Clinic, Vol. 37, June 1962.

The importance of the diagnosis of abdominal aortic aneurysm has increased greatly in the last decade, as surgical methods of correction have been perfected.

Most abdominal aneurysms are arteriosclerotic in origin and occur in males over the age of sixty years. They almost always occur below the origin of the renal arteries. Abdominal pain is of variable character but is often constant and severe, and may extend into the pelvis, back or legs. The expansile pulsating mass is almost always palpable and not uncommonly causes symptoms because of pressure on contiguous structures. X-ray examination of the lumbar region reveals linear calcification within the aortic wall in more than 75% of cases. Aortographic examination is rarely necessary to confirm diagnosis.

With rupture into the GI tract hemetemesis and melena may occur. The fixed 3rd portion of the duodenum is the most common part of the GI tract perforated. With rupture, however rapid, exsangiunation is uncommon — In 63 cases, although 17 died within 6 hours and 29 died within 24 hours, 4 lived longer than one month and 1 survived 6 weeks.

Amphotericin B: Is It Nephrotoxic? Amer. Journ. Med., Vol. 33, July 1962.

Amphotericin B is used in systemic fungal infections and is the most effective drug known for the treatment of histoplasmosis, blastomycosis, cryptococcus, coccidiidomycosis, aspergillosis, sporotrichosis, chromoblastomycosis and candidiasis. It is accompanied sometimes by proteinuria, nitrogen retention, and a fall in renal concentrating ability. Studies were performed and it was shown that these effects on the kidney were reversible.

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THE MECHANISM AND CONTROL OF NAUSEA AND VOMITING — dealing with the symptoms and control of nausea and vomiting in the light of significant knowledge acquired during the past ten years.

The above 16 mm. films are in colour and sound. Showings may be arranged by writing to: The Medical Film Center, Smith Kline & French Inter-American Corporation, 300 Laurentian Blvd., Montreal 9, Que.

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